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REVIEW

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# *Capsicum annuum* L. and its bioactive constituents: A critical review of a traditional culinary spice in terms of its modern pharmacological potentials with toxicological issues

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## Abstract

*Capsicum annuum* L., commonly known as chili pepper, is used as an important spice globally and as a crude drug in many traditional medicine systems. The fruits of *C. annuum* have been used as a tonic, antiseptic, and stimulating agent, to treat dyspepsia, appetites, and flatulence, and to improve digestion and circulation. The article aims to critically review the phytochemical and pharmacological properties of *C. annuum* and its major compounds. Capsaicin, dihydrocapsaicin, and some carotenoids are reported as the major active compounds with several pharmacological potentials especially as anticancer and cardioprotectant. The anticancer effect of capsaicinoids is mainly mediated through mechanisms involving the interaction of $Ca^{2+}$-dependent activation of the MAPK pathway, suppression of NOX-dependent reactive oxygen species generation, and p53-mediated activation of mitochondrial apoptosis in cancer cells. Similarly, the cardioprotective effects of capsaicinoids are mediated through their interaction with cellular transient receptor potential vanilloid 1 channel, and restoration of calcitonin gene-related peptide via $Ca^{2+}$-dependent release of neuropeptides and suppression of bradykinin. In conclusion, this comprehensive review presents detailed information about the traditional uses, phytochemistry, and pharmacology of major bioactive principles of *C. annuum* with special emphasis on anticancer, cardioprotective effects, and plausible toxic adversities along with food safety.

**KEYWORDS**
anticancer, capsaicinoids, *Capsicum annuum*, cardioprotective, pharmacology, traditional use

## 1 | INTRODUCTION

Medicinal plants and their phytochemicals play important role in the maintenance of human health. Apart from being an integral part of traditional medicines all over the world, medicinal plants also serve as an important source for the discovery and development of modern medicines (Atanasov et al., 2015; Fitzgerald, Heinrich, & Booker, 2020; Newman & Cragg, 2020). Various medicinal plants are also used as food ingredients and spices for well-known health benefits. Similarly, many compounds isolated from these traditional spices have received great attention in recent years due to their potential role in the prevention and treatment of several diseases (Khanal et al., 2021).

*Capsicum annuum* L. (Family: Solanaceae; Figure 1) is one such medicinal plant that has been used as a traditional culinary spice for hundreds of years and is extensively studied due to the presence of many bioactive compounds such as capsaicin. The genus *Capsicum* consists of around 22 species and has a long history of cultivation

  


**FIGURE 1** Fruits of *Capsicum annuum* L. (a) fruits with flowers; (b) twigs with fruits; (c,d) whole plant showing the ripened *C. annuum* fruits; and (e) dried *C. annuum* fruit. The photographs are recorded by authors

dating back more than 7000 years ago (Hui, 2006). Five species of *Capsicum* namely *C. annuum*, *C. baccatum*, *C. chinense*, *C. frutescens*, and *C. pubescens* are widely cultivated along with other varieties (Hui, 2006; Khoury et al., 2020). While *C. annuum* is among the most economically important species (Jaiswal, Gahlaut, Kumar, & Ramchiary, 2021). *C. annuum* is native to South Central America and is cultivated in tropical as well as subtropical countries of Africa and Asia (Farooqi, Sreeramu, & Srinivasappa, 2005; Hernández-Pérez, del Rocío Gómez-García, Valverde, & Paredes-López, 2020), while it is now cultivated throughout the warmer regions of the world (NIIR Board, 2004). In Asia, it is mainly cultivated in India sub-continental, South-East Asia, and Japan; in North America, it is cultivated in Mexico, Canada, the United States, and in Europe, it is cultivated in Italy, Turkey, Portugal, and so on (Devi et al., 2021; Farooqi et al., 2005). Chili has been incorporated into most of the cuisines of the world for its characteristic flavor and pungency for centuries (Yang, Chung, & Kwon, 2017). In the United States, it has been cultivated since 1600 when Spanish colonists grew it in northern New Mexico (Hernández-Pérez et al., 2020). Probably Portuguese introduced the chili to India directly from America (Farooqi et al., 2005). India is a major chili producer, where it is cultivated in almost all the regional states. Andhra Pradesh has been reported to be the highest chili-growing state in India. The major chili cultivating states of India are Arunachal Pradesh, Karnataka, Maharashtra, and Punjab (Devi et al., 2021; Farooqi et al., 2005). Indian chilies are marketed and distributed in over 90 countries of the world (Devi et al., 2021; Farooqi et al., 2005; J. Zhang et al., 2019).

Having worldwide distribution, *C. annuum* is known by various vernacular names such as bell pepper, pod pepper, sweet pepper, cayenne pepper, and red pepper in English (Khoury et al., 2020; T. Lim, 2013; Seidemann, 2005). In India, it is regionally known by various local names such as *Marichiphalam*; *Katuvira*; *Bruhi* in Sanskrit; *Lal-mirchi*, *Gach-mirchi* in Hindi; *Lalmirchi*, *Lanka-march* in Bengali, and so on (Baruah & Lal, 2020; Khan, Mahmood, Ali, Saeed, & Maalik, 2014; Unal & Islek, 2019). The fruits of *C. annuum* occupy a significant place in the treatment of various kinds of diseases in traditional systems of medicine ranging from inflammatory diseases in cardiovascular and gastric systems and in cancers. After being introduced into Europe, in 1597, John Gerard mentioned that it has "deobstruent" action to prevent the king's evil swelling. In the eighteenth and nineteenth centuries, it was considered a stimulating agent (Crellin & Philpott, 1990). In 1853, J.W. Comfort mentioned the *Capsicum* in "*The Practice of Medicine on Thomsonian Principles*" for the treatment of dropsy, rheumatism, stimulating blood flow, and inducing warmth (Jolayemi, 2017). The Dispensary of the United States of America in 1943 mentioned that *Capsicum* is a powerful local stimulant. Several remedial options have been used as an Ayurvedic herb in the Indian traditional medicinal system (Batiha et al., 2020). The fruits of

*C. annuum* have been used as a tonic, antiseptic, stimulating agent, and to treat dyspepsia, appetite, and flatulence, and to improve digestion and circulation.

Various scientific articles have recently reported the potent cardiovascular protective activities of *Capsicum* and its constituents, especially capsaicin. Cardiovascular diseases (CVD) rank first in the worldwide mortality ratio as compared to other health complications (Mendis, Puska, Norrving, & Organization, 2011). One of the recent reports by the American College of Cardiology states that about 17.8 million deaths worldwide were due to CVDs and WHO projected that the CVD-associated mortality would be around 24 million by 2030 (Kyu et al., 2018; Roth et al., 2018; Sanati, Razavi, & Hosseinzadeh, 2018). CVD is a serious chronic multifactorial disease that adversely affects the health, well-being, and lifestyle of an individual (Nathan, 2015). Coronary artery disease is one such subset of CVD caused by the blockage of coronary arteries. This lead to the lack of oxygen and nutrients that cause the death of cardiomyocytes in the heart and results in heart failure (Kitmitto, Baudoin, & Cartwright, 2019). Some of the major causes of CVD are primarily associated with increased or altered triglyceride contents, elevated blood pressure, physical inactivity, and use of alcohol and tobacco, and so on. Individuals with type 2 diabetes mellitus have been largely regarded as a high-risk population for CVD onset. Thus, preventing the risk of CVD is a timely task. Consistent with this view, a growing number of studies are focusing toward natural products as safe alternatives for treating and managing patients with cardio-metabolic disorders. Along with several other medicinal plants, *C. annuum* and its compound such as capsaicinoids have been reported to elicit tremendous potential for the management of CVD (Batiha et al., 2020).

In recent years, there is a growing interest in the *C. annuum* and its bioactive compounds including capsaicin in relation to their potent pharmacological activities. Capsaicin has been reported with a wide number of traditional as well as pharmacological uses which includes antioxidant, immunomodulatory, anticancer, antimutagenic, antiplatelet, antiangiogenic, cardiovascular, antihyperlipidemic, energy metabolic, gastroprotective, hypothermic, antiinflammatory, pain modulating, antiischemic, antiarrhythmic, antiviral, antidiabetic, thermogenic and weight-reducing, and antiulcer activity. A meticulous search on the Scopus database (www.scopus.com, accessed on October 25, 2021) showed a total of 9,656 results for "*Capsicum annuum*" and 23,992 results for capsaicin. These numbers of publications have gradually increased after 1990 (Figure 2). However, most of the scientific information, abundant yet scattered, needed a comprehensive critical review regarding its bioactive chemical

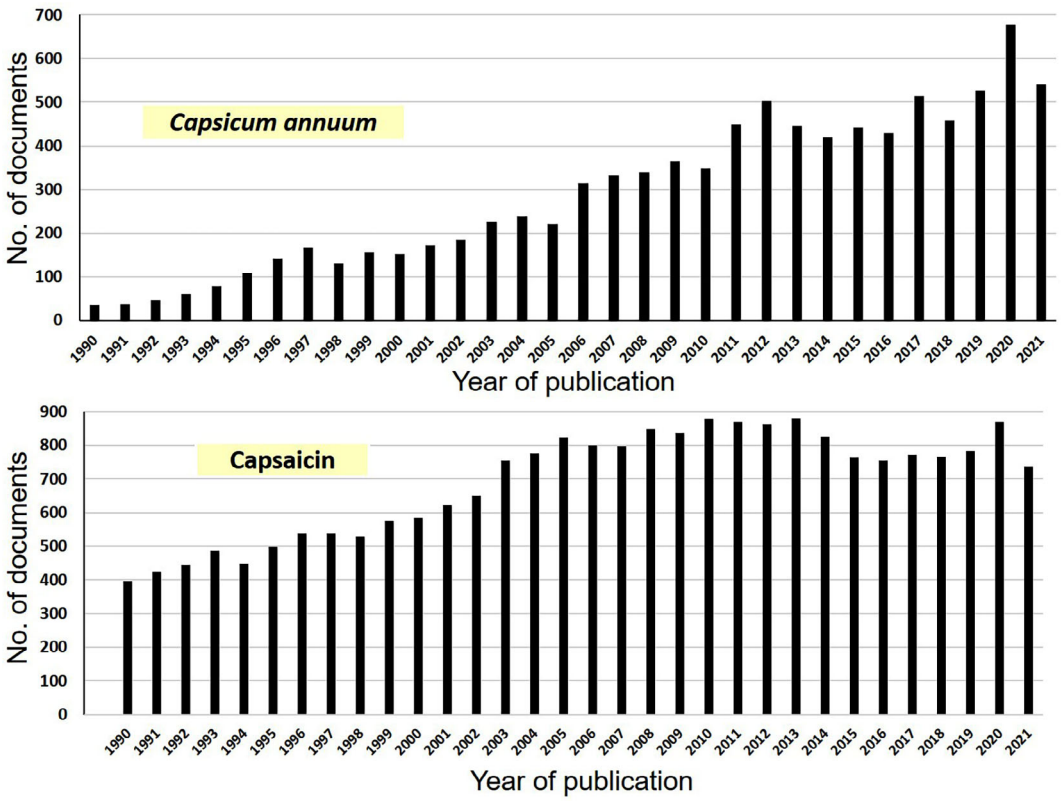


**FIGURE 2** Trends in *Capsicum annuum* as well as capsaicin research. (a) Number of publications of *C. annuum* per year from 1990 onward; this information's main subject areas were Pharmacology, Toxicology, Pharmaceutics, Agricultural and Biological Sciences, Chemistry, and so on and it has been observed that the numbers of publications have gradually increased after 1990. *Source*: www.scopus.com, accessed on October 25, 2021.(b) Number of publications of capsaicin per year from 1990 onward; this information main subject areas were Pharmacology, Toxicology, Pharmaceutics, Agricultural and Biological Sciences, Chemistry, and so on and it has been observed that the numbers of publications have gradually increased after 1990. *Source*: www.scopus.com, accessed on October 25, 2021

constituents and their relation to pharmacological activities with elaborations of the detailed mechanisms. To understand the current status of chemical and pharmacological research related to *C. annum*, a critical analysis of documented scientific information was conducted and reviewed the history, traditional uses, phytoconstituents, pharmacological activities, and therapeutic potential of *C. annuum* fruits along with various pharmacological activities of capsaicin. This critical review summarized the current knowledge on diverse biological targets of capsaicin and the mode of action of capsaicin and a few other isolated phytochemicals from *C. annuum* against different human ailments. The literature covered the reported research work or handbook on *C. annuum* and the major bioactive constituent capsaicin from the year 1973 to 2021 with the major portion of information pertaining since 2007. The information collected from the reputed international electronic databases and resources were utilized in emphasizing the biological and pharmacological properties of *C. annuum* and capsaicinoids with a special focus toward CVD.

## 2 | METHODOLOGY

For this review work, high-quality publications related to *C. annuum* and capsaicin published till October 2021 were collected from various scientific databases including PubMed, Scopus, Science Direct, SciFinder, and Google Scholar using the various keywords such as "Red pepper" or "*Capsicum annuum*" or "*Capsicum*" or "capsaicin" in combination with "constituents," "traditional uses," "drug interactions," "pharmacological activity," "biological activity," "in vitro," "in vivo," "clinical studies," "pharmacokinetics," "food safety," and "toxicity." At first, the abstracts of all publications were collected and examined. Then, all the relevant full-length articles were collected and analyzed, and a conclusion was made concerning its incorporation for further analysis for the review work. Only peer-reviewed high-quality English language journals were included in this study.

## 3 | PHYTOCHEMISTRY OF *C. annuum*

The *C. annuum* (red pepper) is an economically valuable agricultural crop and is a very good dietary source of natural pigments and antioxidant phytochemicals (Silva et al., 2014). The fruits of *C. annuum* are the rich sources of several bioactive classes of phytochemicals including carotenoids, polyphenolic compounds including phenolic acids and flavonoids, saponins, capsaicinoids, vitamins C, E, and A, and volatile compounds (de Sá Mendes & de Andrade Gonçalves, 2020; Gregory, Chen, & Philip, 1987; Iorizzi et al., 2001; Lemos, Reimer, & Wormit, 2019; Marín, Ferreres, Tomás-Barberán, & Gil, 2004; McKenna, Jones, Hughes, & Tyler, 2012; Mokhtar et al., 2015; Naef, Velluz, & Jaquier, 2008; Rodrigues, Nicácio, Jardim, Visentainer, & Maldaner, 2019; Sandoval-Castro et al., 2017; Yamauchi, Aizawa, Inakuma, & Kato, 2001). There are more than 300 phytoconstituents isolated till now from *C. annuum*. The most bioactive important and predominant pungent phytoconstituent of *C. annuum* is capsaicin (McKenna et al., 2012). A series of homologous branched- and straight-chain alkyl vanillylamides known as capsaicinoids are present in the fruit extract of *C. annuum*. Most of the important capsaicinoids included capsaicin (**1**) (48.6%), dihydrocapsaicin (**2**) (36%), nordihydrocapsaicin (**3**) (7.4%), homodihydrocapsaicin (**4**) (2%), and homocapsaicin (**5**) (2%) (Figure 3; McKenna et al., 2012). The major bioactive phenolic compounds in *C. annuum* included 4-hydroxybenzoic acid (**6**), gallic acid (**7**), vanillic acid (**8**), caffeic acid (**9**), *p*-coumaric acid (**10**), chlorogenic acid (**11**), sinapic acid (**12**), ferulic acid (**13**), ellagic acid (**14**), *trans*-*p*-sinapoyl-$\beta$-D-glucopyranoside (**15**), *trans*-p-feruloyl-$\beta$-D-glucopyranoside (**16**), capsaicin (**1**), and dihydrocapsaicin (**2**) (Figure 3; Hallmann & Rembiałkowska, 2012; Materska & Perucka, 2005; Rodrigues et al., 2019; Sandoval-Castro et al., 2017). The methanolic extract of the fruits of *C. annuum* are also rich source of various polyphenolic compounds (Mokhtar et al., 2015). It is reported that the most important bioactive flavonoids present in *C. annuum* are the aglycones and glycosides of myricetin, quercetin, luteolin, apigenin, and kaempferol (de Sá Mendes & de Andrade Gonçalves, 2020; Juániz et al., 2016). The major bioactive flavonoids in the fresh *C. annuum* included as quercetin 3-*O*-$\alpha$-L-rhamnopyranoside (**17**), quercetin glucoside (**18**), kaempferol diglucoside (**19**), luteolin glucoside (**20**), quercetin (**21**), rutin (**22**), naringenin (**23**), catechin (**24**), and epicatechin (**25**) (Figure 4; Materska & Perucka, 2005; Mokhtar et al., 2015; Rodrigues et al., 2019; Sandoval-Castro et al., 2017). The main constituent of *C. annuum* is quercetin 3-*O*-$\alpha$-L-rhamnopyranoside having significant antiradical potentials (Materska & Perucka, 2005). A novel antioxidant capsaicin derivative named 6″,7″-dihydro-5′,5‴-dicapsaicin along with a known metabolite, $\omega$-hydroxycapsaicin has also been reported from the fruits of *C. annuum* (Ochi, Takaishi, Kogure, & Yamauti, 2003). A list of diverse major classes of phytochemicals present in the different parts of *C. annuum* is given in Table 1.

The hot hydroalcoholic (methanol:water; 70:30) extract of the fruits of *C. annuum* are used to isolate the different bioactive compounds and the methods used were liquid chromatography (LC) and preparative high-performance liquid chromatography (HPLC). The reported several bioactive phenolic compounds are *trans*-*p*-feruloyl-$\beta$-D-glucopyranoside, *trans*-*p*-feruloyl alcohol-4-*O*-[6-(2-methyl-3-hydroxypropionyl)] glucopyranoside, *trans*-*p*-sinapoyl-$\beta$-D-glucopyranoside, apigenin 6-*C*-$\beta$-D-glucopyranoside-8-*C*-$\alpha$-L-arabinopyranoside, quercetin 3-*O*-$\alpha$-L-rhamnopyranoside-7-*O*-$\beta$-D-glucopyranoside, lutoeolin 7-O-[2-($\beta$-D-apiofuranosyl)-$\beta$-D-glucopyranoside], luteolin 6-*C*-$\beta$-D-glucopyranoside-8-*C*-$\alpha$-L-arabinopyranoside, quercetin 3-*O*-$\alpha$-L-rhamnopyranoside, and luteolin 7-O-[2-($\beta$-D-apiofuranosyl)-4-($\beta$-D-glucopyranosyl)-6-malonyl]-$\beta$-D-glucopyranoside (Je ong et al., 2011; Materska et al., 2003; Materska & Perucka, 2005). The ultra-high-performance liquid chromatography coupled with linear ion trap quadrupole Orbitrap (LTQ-OrbiTrap) mass spectrometry analysis of the methanolic extract of *C. annuum* fruit has reported the presence of 49 polyphenolic constituents and out of that five compounds, namely 5-*O*-*p*-coumaroylquinic acid, quercetin 3-*O*-(2″-*O*-hexosyl)rhamnoside, luteolin 7-*O*-(2″-*O*-pentosyl-4″-*O*-hexosyl)

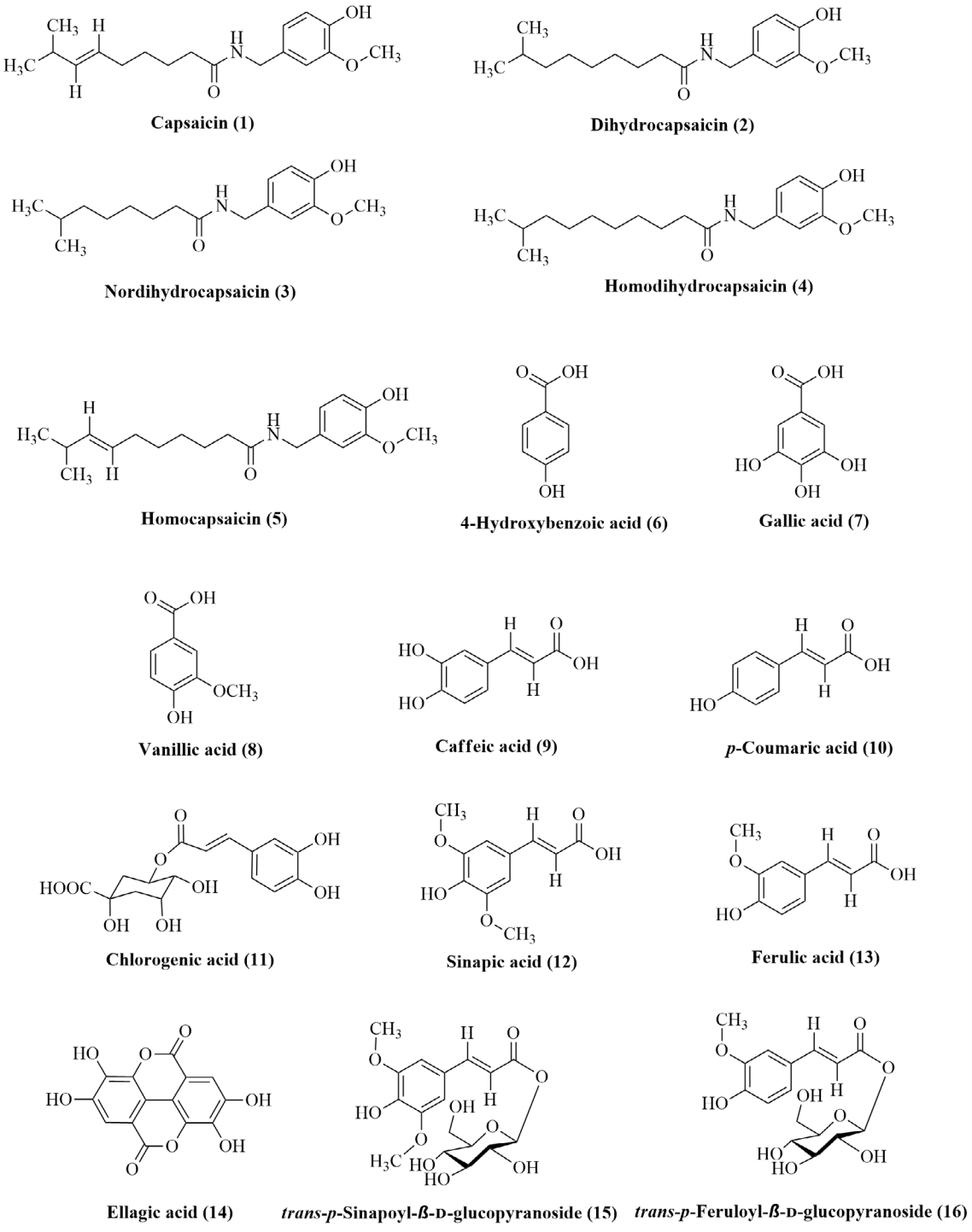


**FIGURE 3** Chemical structures of major bioactive phenolic compounds present in the fruits of *Capsicum annuum* L.

hexoside, isorhamnetin 3-*O*-[6″-*O*-(5-hydroxyferuloyl)hexoside]-7-*O*-rhamnoside, and luteolin 7-*O*-[2″-*O*-(5‴-*O*-sinapoyl)pentosyl-6″-*O*-malonyl]hexoside were reported for the first time in red peppers (Mudrić et al., 2017). The high-performance anion-exchange chromatography coupled with pulsed amperometric detection analysis of the methanolic extract of the fruits of *C. annuum* has reported the presence of 13 carbohydrate constituents (Mudrić et al., 2017).

Like ripe *C. annuum* fruits, the green mature fruits also contain various glycosides. The HPLC coupled with diode array detection-electrospray ionization-mass spectrometry analysis of the green mature fruits of hydroalcoholic extract in the ratio of methanol and water (70:30) of sweet *C. annuum* L. reported the existence of five antioxidant hydroxycinnamic derivatives along with 23 flavonoid constituents (Marín et al., 2004). It is reported that the immature green

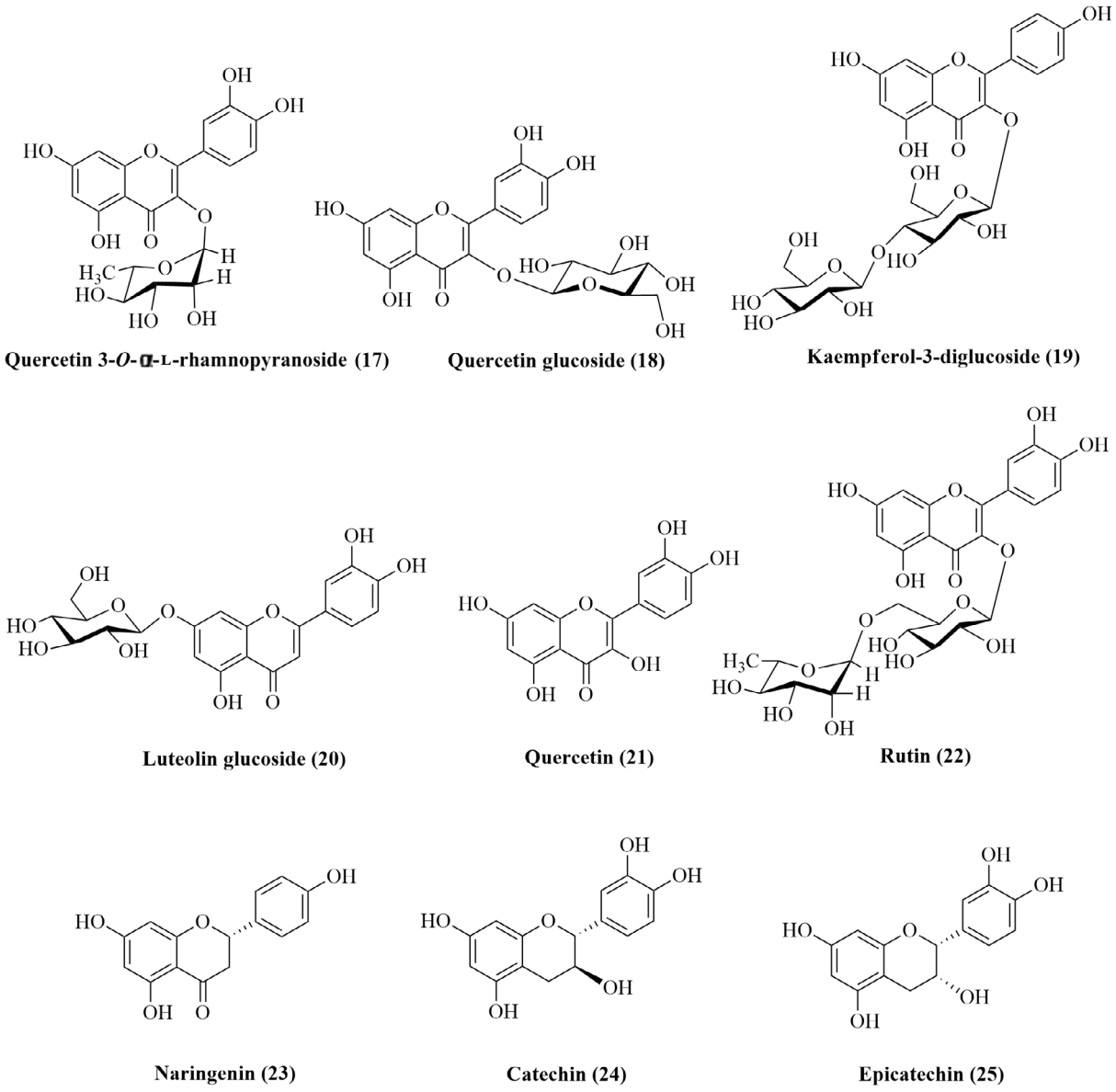


**FIGURE 4** Chemical structures of various major bioactive flavonoid constituents present in the fresh fruits of *Capsicum annuum* L.

peppers had a very high content of phenolic compounds followed by green, immature red, and red ripe *C. annuum* (Marín et al., 2004; Tundis et al., 2013). The main vitamin C constituent in *C. annuum* is ascorbic acid (**26**), and its amount increased as the pepper reached maturity (Figure 5; Q. Iqbal, Amjad, Asi, & Ariño, 2013; Marín et al., 2004). The red ripe fruits of hydroalcoholic extract (methanol: water; 70:30) of *C. annuum* contained the highest amount of vitamin C and provitamin A (Marín et al., 2004). The major provitamin A constituents in *C. annuum* are $\beta$-carotene (**27**) and $\beta$-cryptoxanthin (**28**) (Figure 5; Hervert-Hernandez, Sayago-Ayerdi, & Goñi, 2010; Marín et al., 2004). A large number of flavone *C*-glycosides were also reported from the fruits of sweet *C. annuum* (Marín et al., 2004). Several bioactive glycosides have been reported from the fruits of *C. annuum*. Higashiguchi and co-workers reported the presence of two glycosides namely capsaicin-$\beta$-D-glucopyranoside and dihydrocapsaicin-$\beta$-D-glucopyranoside from the fruits of *C. annuum* (Higashiguchi, Nakamura, Hayashi, & Kometani, 2006). De Marino et al. reported the presence of four new acyclic diterpene glycosides (capsianosides) such as capsianoside VIII, capsianoside IX, capsianoside I ester, and capsianoside L, along with other 12 known phytochemicals from the methanolic extract of fresh sweet fruits of *C. annuum*. Other glycosides, namely capsianosides II, III, VII, X, XIII, XV, XVI, A, B, C, D, E, and F were also identified in the dried ripe red pepper fruits (De Marino et al., 2006; Iorizzi et al., 2001; J.-H. Lee, Kiyota, Ikeda, & Nohara, 2006; J.-H. Lee, Kiyota, Ikeda, & Nohara, 2007). The ethyl acetate fraction of the fruits of *C. annuum* reported the presence of two novel capsaicinoid type compounds named capsiate and dihydrocapsiate along with a new nordihydrocapsiate (Kobata, Todo, Yazawa, Iwai, & Watanabe, 1998; Kobata et al., 1999). The chemical name of the capsiate was reported as

**TABLE 1** Various major classes of phytochemicals present in different parts of *C. annuum* L. (red pepper)

| Phytochemicals | Extract/part used | References |
|---|---|---|
| I. *Phenolic compounds* | | |
| 2-Methoxy-2-phenylacetic acid | Fruits | de Sá Mendes and de Andrade Gonçalves (2020) |
| 4-Vinylphenol | Fruits | de Sá Mendes and de Andrade Gonçalves (2020) |
| 5-*O*-Caffeoylquinic acid | MeOH extract/fruits | Silva et al. (2014); Mudrić et al. (2017) |
| 5-*O*-*p*-Coumaroylquinic acid | MeOH extract/fruits | Mudrić et al. (2017) |
| Aesculin | MeOH extract/fruits | Mudrić et al. (2017) |
| Caffeic acid 4-*O*-hexoside | MeOH extract/fruits | Mudrić et al. (2017) |
| Caffeic acid derivative | MeOH:water extract/fruits | Marín et al. (2004) |
| Caffeic acid glucoside I | Fruits | Juániz et al. (2016) |
| Caffeic acid glucoside II | Fruits | Juániz et al. (2016) |
| Caffeoyl glucoside | MeOH extract/fruits | Mokhtar et al. (2015) |
| Caffeoyl-*O*-hexoside | Fruits | D. Zhang et al. (2021) |
| Chlorogenic acid | Fruits | Hallmann and Rembiałkowska (2012) |
| Cinnamic acid | MeOH extract/fruits | Mudrić et al. (2017) |
| *cis*-*p*-Coumaric acid 4-*O*-*β*-D-glucoside | MeOH extract/fruits | Iorizzi et al. (2001) |
| Conyferyl aldehyde | MeOH extract/fruits | Mudrić et al. (2017) |
| Daphnetine | MeOH extract/fruits | Mokhtar et al. (2015) |
| Ferulic acid 4-*O*-hexoside | MeOH extract/fruits | Mudrić et al. (2017) |
| Feruloyl hexoside | MeOH:water extract/fruits | Jeong et al. (2011) |
| Feruloyl-*O*-glucoside | Fruits | D. Zhang et al. (2021) |
| Gallic acid | MeOH extract/fruits | Mudrić et al. (2017) |
| Guaiacol | Fruits | de Sá Mendes and de Andrade Gonçalves (2020) |
| Hydrocaffeic acid | MeOH extract/fruits | Mokhtar et al. (2015) |
| Hydroxybenzoylhexose | MeOH extract/fruits | Mokhtar et al. (2015); D. Zhang et al. (2021) |
| Icariside $E_5$ | MeOH extract/fruits | Iorizzi et al. (2001) |
| Isovanillic acid | Fruits | de Sá Mendes and de Andrade Gonçalves (2020) |
| Isovanillin | Fruits | de Sá Mendes and de Andrade Gonçalves (2020) |
| Methylparaben | Fruits | de Sá Mendes and de Andrade Gonçalves (2020) |
| *N*-Caffeoyl putrescine | Fruits | D. Zhang et al. (2021) |
| Paeonol | Fruits | de Sá Mendes and de Andrade Gonçalves (2020) |
| *p*-Coumaric acid | MeOH extract/fruits | Mudrić et al. (2017) |
| *p*-Coumaric acid 4-*O*-hexoside | MeOH extract/fruits | Mudrić et al. (2017) |
| *P*-Coumaroyl glycolic acid | MeOH extract/fruits | Mokhtar et al. (2015) |
| *P*-Coumaryl tyrosine | MeOH extract/fruits | Mokhtar et al. (2015) |
| *p*-Hydroxybenzoic acid | MeOH extract/fruits | Mudrić et al. (2017) |
| *p*-Hydroxyphenylacetic acid | MeOH extract/fruits | Mudrić et al. (2017) |
| Protocatechuic acid | MeOH extract/fruits | Mudrić et al. (2017) |
| Pyrogallol | Fruits | de Sá Mendes and de Andrade Gonçalves (2020) |
| Sinapic acid 4-*O*-hexoside | MeOH extract/fruits | Mudrić et al. (2017) |
| Sinapoyl hexoside | MeOH:water extract/fruits | Jeong et al. (2011) |
| Syringic acid | MeOH extract/fruits | Mudrić et al. (2017) |
| *trans*-*p*-Coumaroyl-*β*-D-glucopyranoside | MeOH:water extract/fruits | Marín et al. (2004) |
| *trans*-*p*-Feruloyl-*β*-D-glucopyranoside | MeOH:water extract/fruits | Marín et al. (2004); de Sá Mendes and de Andrade Gonçalves (2020) |
| *trans*-*p*-Sinapoyl-*β*-D-glucopyranoside | MeOH extract/fruits | Iorizzi et al. (2001); Marín et al. (2004); de Sá Mendes and de Andrade Gonçalves (2020); D. Zhang et al. (2021) |
| Umbelliferone | MeOH extract/fruits | Mudrić et al. (2017) |

(Continues)

**TABLE 1** (Continued)

| Phytochemicals | Extract/part used | References |
|---|---|---|
| Vanillic acid glucoside | MeOH extract/fruits | Mokhtar et al. (2015) |
| Vanillin | MeOH extract/fruits | Mudrić et al. (2017) |
| Vanilloyl $\beta$-D-glucoside | MeOH extract/fruits | Iorizzi et al. (2001) |
| II. *Flavonoids* | | |
| Apigenin | MeOH:water extract; MeOH extract/fruits | Mudrić et al. (2017) |
| Apigenin 6,8-di-*C*-hexoside | MeOH:water extract; MeOH extract/fruits | Marín et al. (2004); Mudrić et al. (2017) |
| Apigenin 6-*C*-hexoside-8-*C*-pentoside | MeOH:water extract; MeOH extract/fruits | Marín et al. (2004); Mudrić et al. (2017) |
| Apigenin 6-*C*-pentoside-8-*C*-hexoside | MeOH:water extract; MeOH extract/fruits | Marín et al. (2004); Mudrić et al. (2017) |
| Apigenin *C*-pentosyl-*C*-hexoside | MeOH:water extract/fruits | Jeong et al. (2011) |
| Apigenin-6-*C*-glucopyranoside-8-*C*-arabinopyranoside | Fruits | D. Zhang et al. (2021) |
| Apigenin-7-*O*-(2″-*O*-apiosyl) glucoside (Apiin) | MeOH extract/fruits | Mudrić et al. (2017); D. Zhang et al. (2021) |
| Chrysoeriol 6,8-di-*C*-hexoside | MeOH:water extract/fruits | Marín et al. (2004) |
| Chrysoeriol 6-*C*-hexoside-8-*C*-pentoside | MeOH:water extract/fruits | Marín et al. (2004) |
| Chrysoeriol 7-*O*-(2-apiosyl-6-acetyl) glucoside | MeOH:water extract/fruits | Marín et al. (2004) |
| Cynaroside (luteolin 7-*O*-glucoside) | MeOH extract/fruits | Silva et al. (2014); Mudrić et al. (2017) |
| Hyperoside (quercetin 3-*O*-galactoside) | MeOH extract/fruits | Mudrić et al. (2017) |
| Isorhamnetin 3-*O*-[6″-*O*-(5-hydroxyferuloyl)hexoside]-7-*O*-rhamnoside | MeOH extract/fruits | Mudrić et al. (2017) |
| Isoscoparin | MeOH:water extract/fruits | Jeong et al. (2011) |
| Kaempferol | Fruits | Hallmann and Rembiałkowska (2012) |
| Kaempferol diglucoside | MeOH extract/fruits | Mokhtar et al. (2015) |
| Kaempferol pentosyldihexoside | MeOH:water extract/fruits | Jeong et al. (2011) |
| Kaempferol-3-*O*-sophoroside | Fruits | de Sá Mendes and de Andrade Gonçalves (2020) |
| Luteolin | MeOH extract/fruits | Mudrić et al. (2017) |
| Luteolin 6,8-di-*C*-glucoside | MeOH:water extract; MeOH extract/fruits | Marín et al. (2004); Jeong et al. (2011); Juániz et al. (2016); Mudrić et al. (2017) |
| Luteolin 6-*C*-(6-malonyl)hexoside-8-*C*-hexoside | MeOH:water extract/fruits | Marín et al. (2004) |
| Luteolin 6-*C*-(6-malonyl)-hexoside-8-*C*-pentoside | MeOH:water extract/fruits | Marín et al. (2004) |
| Luteolin 6-*C*-hexoside | MeOH:water extract; MeOH extract/fruits | Marín et al. (2004); Mudrić et al. (2017) |
| Luteolin 6-*C*-hexoside-8-*C*-pentoside | MeOH:water extract; MeOH extract/fruits | Marín et al. (2004); Juániz et al. (2016); Mudrić et al. (2017) |
| Luteolin 6-*C*-hexoside-8-*C*-rhamnoside | MeOH:water extract/fruits | Marín et al. (2004) |
| Luteolin 6-*C*-pentoside-8-*C*-hexoside | Fruits | Marín et al. (2004); Juániz et al. (2016); Mudrić et al. (2017) |
| Luteolin 6-*C*-rhamnoside-8-*C*-hexoside | Fruits | Marín et al. (2004) |
| Luteolin 6-*C*-$\beta$-D-glucopyranoside-8-*C*-$\alpha$-L-arabinopyranoside | Fruits | de Sá Mendes and de Andrade Gonçalves (2020) |
| Luteolin 7-*O*-(2-apiosyl)glucoside | MeOH:water extract/fruits | Marín et al. (2004) |
| Luteolin 7-*O*-(2-apiosyl-6- malonyl) glucoside I | Fruits | Juániz et al. (2016) |

**TABLE 1** (Continued)

| Phytochemicals | Extract/part used | References |
|---|---|---|
| Luteolin 7-*O*-(2-apiosyl-6- malonyl) glucoside II | Fruits | Juániz et al. (2016) |
| Luteolin 7-*O*-(2-apiosyl-6-acetyl) glucoside | MeOH:water extract/fruits | Marín et al. (2004) |
| Luteolin 7-*O*-(2-apiosyl-6-malonyl) glucoside | MeOH:water extract/fruits | Marín et al. (2004) |
| Luteolin 7-*O*-(2-apiosyldiacetyl) glucoside | MeOH:water extract/fruits | Marín et al. (2004) |
| Luteolin 7-*O*-(2″-*O*-pentosyl) hexoside | MeOH extract/fruits | Mudrić et al. (2017) |
| Luteolin 7-*O*-(2″-*O*-pentosyl-4″-*O*-hexosyl) hexoside | MeOH extract/fruits | Mudrić et al. (2017) |
| Luteolin 7-*O*-(2″-*O*-pentosyl-4″-*O*-hexosyl-6″-*O*-malonyl) hexoside | MeOH extract/fruits | Mudrić et al. (2017) |
| Luteolin 7-*O*-(2″-*O*-pentosyl-6″-*O*-malonyl) hexoside | MeOH extract/fruits | Mudrić et al. (2017) |
| Luteolin 7-*O*-[2-(*β*-D-apiosyl)-4-(*β*-D-glucosyl)-6-malonyl]-*β*-D-glucoside | Fruits | de Sá Mendes and de Andrade Gonçalves (2020) |
| Luteolin 7-*O*-[2-(*β*-D-apiosyl)-*β*-D-glucoside] | Fruits | de Sá Mendes and de Andrade Gonçalves (2020) |
| Luteolin 7-*O*-[2″-*O*-(5‴-*O*-sinapoyl) pentosyl] hexoside | MeOH extract/fruits | Mudrić et al. (2017) |
| Luteolin 7-*O*-[2″-*O*-(5‴-*O*-sinapoyl) pentosyl-6″-*O*-malonyl] hexoside | MeOH extract/fruits | Mudrić et al. (2017) |
| Luteolin 8-*C*-hexoside | MeOH:water extract; MeOH extract/fruits | Marín et al. (2004); Jeong et al. (2011); Mudrić et al. (2017) |
| Luteolin acetylglucoside I | Fruits | Juániz et al. (2016) |
| Luteolin *C*-pentosyl-*C*-hexoside | MeOH:water extract/fruits | Jeong et al. (2011) |
| Luteolin diglucoside | MeOH extract/fruits | Mokhtar et al. (2015) |
| Luteolin glucoside | MeOH extract/fruits | Mokhtar et al. (2015) |
| Luteolin *O*-(apiosyl)hexoside | MeOH:water extract/fruits | Jeong et al. (2011) |
| Luteolin *O*-(apiosylacetyl)glucoside | MeOH:water extract/fruits | Jeong et al. (2011) |
| Luteolin *O*-(apiosylmalonyl)glucoside | MeOH:water extract/fruits | Jeong et al. (2011) |
| Luteolin *O*-malonylpentosyldihexoside | MeOH:water extract/fruits | Jeong et al. (2011) |
| Luteolin-6-*C*-glucoside (Isoorientin) | Fruits | D. Zhang et al. (2021) |
| Luteolin7-*O*-(2-apiosyl) glucoside | Fruits | Juániz et al. (2016) |
| Luteolin-7-*O*-(2-apiosyl-6-acetyl) hexoside | Fruits | de Sá Mendes and de Andrade Gonçalves (2020) |
| Luteolin-7-*O*-(2-apiosyl-6-malonyl) glucoside | Fruits | Silva et al. (2014); de Sá Mendes and de Andrade Gonçalves (2020) |
| Myricetin | Fruits | Hallmann and Rembiałkowska (2012) |
| Myricetin-3-*O*-rhamnoside | Fruits | Silva et al. (2014) |
| Naringenin | MeOH extract/fruits | Mudrić et al. (2017); de Sá Mendes and de Andrade Gonçalves (2020) |
| Naringenin 7-*O*-hexoside | MeOH extract/fruits | Mudrić et al. (2017) |
| Naringenin-7-*O*-glucoside (Prunin) | Fruits | de Sá Mendes and de Andrade Gonçalves (2020) |
| Orientin | MeOH:water extract/fruits | Jeong et al. (2011) |
| Quercetin | MeOH extract/fruits | Hallmann and Rembiałkowska (2012); Mudrić et al. (2017) |
| Quercetin 3-glucoside-7-rhamnoside | Fruits | Juániz et al. (2016) |
| Quercetin 3-*O*-(2″-*O*-hexosyl) rhamnoside | MeOH extract/fruits | Mudrić et al. (2017) |

(Continues)

**TABLE 1** (Continued)

| Phytochemicals | Extract/part used | References |
|---|---|---|
| Quercetin 3-*O*-hexoside | MeOH:water extract/fruits | Jeong et al. (2011) |
| Quercetin 3-*O*-rhamnoside | MeOH:water extract; MeOH extract/fruits | Marín et al. (2004); Mudrić et al. (2017) |
| Quercetin 3-*O*-rhamnoside-7-*O*-glucoside | MeOH:water extract; MeOH extract/fruits | Marín et al. (2004); Mudrić et al. (2017) |
| Quercetin 3-*O*-$\alpha$-L-rhamnopyranoside | Fruits | de Sá Mendes and de Andrade Gonçalves (2020) |
| Quercetin 3-*O*-$\alpha$-L-rhamnoside-7-*O*-$\beta$-D-glucoside | Fruits | de Sá Mendes and de Andrade Gonçalves (2020) |
| Quercetin 3-sambubioside-7-rhamnoside | Fruits | Juániz et al. (2016) |
| Quercetin D-glucoside | Fruits | Hallmann and Rembiałkowska (2012) |
| Quercetin *O*-rhamnosyl-*O*-hexoside | MeOH:water extract/fruits | Jeong et al. (2011) |
| Quercetin rhamnoside | MeOH extract/fruits | Mokhtar et al. (2015) |
| Quercetin-3-*O*-neohesperidoside | Fruits | de Sá Mendes and de Andrade Gonçalves (2020) |
| Quercetin-3-*O*-rutinoside | Fruits | Hallmann and Rembiałkowska (2012); Silva et al. (2014) |
| Quercetin-3-*O*-α-L-rhamnopyranoside | Fruits | D. Zhang et al., 2021 |
| Quercetin 3-*O*-rhamnoside | MeOH extract/fruits | Iorizzi et al. (2002); De Marino et al. (2006) |
| Vicenin-2 | MeOH:water extract/fruits | Jeong et al. (2011) |
| Vitexin (Apigenin 8-*C*-glucoside) | MeOH extract/fruits | Mudrić et al. (2017) |
| III. *Aliphatic glycosides* | | |
| 3-*O*-(9,12,15-octadecatrienoyl) glyceryl $\beta$-D-galactopyranoside | Fruits | De Marino et al. (2006) |
| Blumenol *C*-glucoside | Fruits | De Marino et al. (2006) |
| IV. *Saponin glycosides* | | |
| 22-*O*-Methylcapsicoside A | MeOH extract/seeds | Iorizzi, Lanzotti, Ranalli, De Marino and Zollo et al. (2002) |
| 22-*O*-Methyl-capsicoside D | MeOH extract/seeds | Iorizzi et al. (2002) |
| 22-*O*-Methylcapsicoside G | MeOH extract/seeds | Iorizzi et al. (2002) |
| Capsicoside A | MeOH extract/seeds | Iorizzi et al. (2002) |
| Capsicoside D | MeOH extract/seeds | Iorizzi et al. (2002) |
| Timosaponin I2 | MeOH extract/seeds | Iorizzi et al. (2002) |
| V. *Capsaicinoids and capsianosides* | | |
| Capsaicin | Acetone extract/fruits | Giuffrida et al. (2013) |
| Capsianoside I | MeOH extract/seeds, MeOH extract/fruits | Iorizzi et al. (2002); De Marino et al. (2006) |
| Capsianoside III | MeOH extract/fruits | De Marino et al. (2006) |
| Capsianoside V | MeOH extract/fruits | De Marino et al. (2006) |
| Dihydrocapsaicin | Acetone extract/fruits | Giuffrida et al. (2013) |
| Homocapsaicin-I | Acetone extract/fruits | Giuffrida et al. (2013) |
| Homodihydrocapsaicin-I | Fruits | de Sá Mendes and de Andrade Gonçalves (2020) |
| Nordihydrocapsaicin | Acetone extract/fruits | Giuffrida et al. (2013) |
| *N*-Vanillyl nonanamide | Fruits | de Sá Mendes and de Andrade Gonçalves (2020) |
| VI. *Anthocyanins* | | |
| Cyanidin 3-*O*-glucoside | Fruits | D. Zhang et al. (2021) |
| Cyanidin 3-*O*-malonylhexoside | Fruits | D. Zhang et al. (2021) |
| Cyanidin 3-*O*-rutinoside | Fruits | D. Zhang et al. (2021) |
| Delphinidin 3-*O*-glucoside | Fruits | D. Zhang et al. (2021) |
| Delphinidin-3, 5-diglucoside | Fruits | D. Zhang et al. (2021) |
| Delphinidin-3-*O*-rutinosid | Fruits | D. Zhang et al. (2021) |

**TABLE 1** (Continued)

| Phytochemicals | Extract/part used | References |
|---|---|---|
| Malvidin 3,5-diglucoside | Fruits | D. Zhang et al. (2021) |
| Malvidin 3-*O*-galactoside | Fruits | D. Zhang et al. (2021) |
| Malvidin 3-*O*-glucoside | Fruits | D. Zhang et al. (2021) |
| Peonidin 3-sophorside-5- glucoside | Fruits | D. Zhang et al. (2021) |
| VII. *Carotenoids* | | |
| (13*Z*)-*cis*-*S*-Cryptoxanthin | Acetone extract/fruits | Giuffrida et al. (2013) |
| (9*Z*)-*cis*-$\alpha$-Carotene | Acetone extract/fruits | Giuffrida et al. (2013) |
| 13/13′-*cis*-Capsanthin | MeOH extract/fruits | Deli, Molnár, Matus and Tóth (2001) |
| 13-*cis*-Zeaxanthin | MeOH extract/fruits | Deli et al. (2001) |
| 15-*cis*-Zeaxanthin | MeOH extract/fruits | Deli et al. (2001) |
| 5,6-Diepicapsokarpoxanthin | MeOH extract/fruits | Deli et al. (2001) |
| 5,6-Diepikarpoxanthin | MeOH extract/fruits | Deli et al. (2001) |
| 5,6-Diepilatoxanthin | MeOH extract/fruits | Deli et al. (2001) |
| 6-Epikarpoxanthin | MeOH extract/fruits | Deli et al. (2001) |
| 8*R*-Mutatoxanthin | MeOH extract/fruits | Deli et al. (2001) |
| 8*S*-Mutatoxanthin | MeOH extract/fruits | Deli et al. (2001) |
| 9/9′-*cis*-Capsanthin | MeOH extract/fruits | Deli et al. (2001) |
| 9-*cis*-Zeaxanthin | MeOH extract/fruits | Deli et al. (2001) |
| All-*trans*-lutein | Fruits | de Sá Mendes and de Andrade Gonçalves (2020) |
| Antheraxanthin | MeOH extract; MeOH:water extract; acetone extract/fruits | Deli et al. (2001); Marín et al. (2004); Cserháti (2006); Hallmann and Rembiałkowska (2012); Giuffrida et al. (2013) |
| Antheraxanthin-C12:0 | Acetone extract/fruits | Giuffrida et al. (2013) |
| Antheraxanthin-C14:0 | Acetone extract/fruits | Giuffrida et al. (2013) |
| Apo-8′-carotenal | Fruits | Cserháti (2006) |
| Canthaxanthin | Fruits | Cserháti (2006) |
| Capsanthin | MeOH extract; MeOH:water extract/fruits | Mouly, Gaydou and Corsetti (1999); Deli et al. (2001); Marín et al. (2004); Giuffrida et al. (2013) |
| Capsanthin 3,6-epoxide | MeOH extract/fruits | Deli et al. (2001) |
| Capsanthin 5,6-epoxide | MeOH extract/fruits | Deli et al. (2001) |
| Capsanthin-5,6-epoxy-C14:0 | Acetone extract/fruits | Giuffrida et al. (2013) |
| Capsanthin-C12:0 | Acetone extract/fruits | Giuffrida et al. (2013) |
| Capsanthin-C12:0, C14:0 | Acetone extract/fruits | Giuffrida et al. (2013) |
| Capsanthin-C12:0, C16:0 | Acetone extract/fruits | Giuffrida et al. (2013) |
| Capsanthin-C14:0 | Acetone extract/fruits | Giuffrida et al. (2013) |
| Capsanthin-C14:0, C14:0 | Acetone extract/fruits | Giuffrida et al. (2013) |
| Capsanthin-C14:0, C16:0 | Acetone extract/fruits | Giuffrida et al. (2013) |
| Capsanthin-C16:0 | Acetone extract/fruits | Giuffrida et al. (2013) |
| Capsanthin-C16:0, C16:0 | Acetone extract/fruits | Giuffrida et al. (2013) |
| Capsanthone | MeOH extract/fruits | Deli et al. (2001) |
| Capsolutein | MeOH extract; MeOH:water extract/fruits | Deli et al. (2001); Marín et al. (2004); de Sá Mendes and de Andrade Gonçalves (2020) |
| *cis*-$\beta$-Carotene | MeOH extract/fruits | Deli et al. (2001); Hallmann and Rembialkowska (2012) |
| *cis*-Capsanthin | MeOH:water extract; acetone extract/fruits | Marín et al. (2004); Giuffrida et al. (2013) |
| *cis*-Capsanthin-C12:0 | Acetone extract/fruits | Giuffrida et al. (2013) |
| *Cis*-Capsanthin-C14:0 | Acetone extract/fruits | Giuffrida et al. (2013) |
| *cis*-Cryptoxanthin | MeOH extract/fruits | Deli et al. (2001) |

(Continues)

**TABLE 1** (Continued)

| Phytochemicals | Extract/part used | References |
|---|---|---|
| *cis*-Lutein | MeOH:water extract/fruits | Marín et al. (2004) |
| *cis*-Zeaxanthin | MeOH:water extract/fruits | Marín et al. (2004); Hallmann and Rembialkowska (2012) |
| Cryptocapsin | MeOH extract/fruits | Deli et al. (2001); Cserháti (2006) |
| Cryptocapsin-C14:0 | Acetone extract/fruits | Giuffrida et al. (2013) |
| Cryptoflavin | Fruits | Hallmann and Rembialkowska (2012) |
| Cryptoxanthin | Fruits | Hallmann and Rembialkowska (2012) |
| Cryptoxanthin-5,6-epoxide | Acetone extract/fruits | Giuffrida et al. (2013) |
| Cucurbitachrome | MeOH extract/fruits | Deli et al. (2001) |
| Cucurbitaxanthin A | MeOH extract; MeOH:water extract/fruits | Deli et al. (2001); Marín et al. (2004) |
| Cucurbitaxanthin B | MeOH extract/fruits | Deli et al. (2001) |
| Cyclovioxanthin | Fruits | Cserháti (2006) |
| Latoxanthin | Fruits | Cserháti (2006) |
| Lutcoxanthin | Fruits | Cserháti (2006) |
| Lutein | MeOH:water extract/fruits | Mouly et al. (1999); Marín et al. (2004) |
| Mutatoxanthin | Fruits | Mouly et al. (1999); Cserháti (2006); de Sá Mendes and de Andrade Gonçalves (2020) |
| Neoxanthin | MeOH extract; MeOH:water extract/fruits | Deli et al. (2001); Marín et al. (2004); de Sá Mendes and de Andrade Gonçalves (2020) |
| Nigroxanthin | MeOH extract/fruits | Deli et al. (2001) |
| Phytoene | Acetone extract/fruits | Giuffrida et al. (2013) |
| Phytofluene | Acetone extract/fruits | Giuffrida et al. (2013) |
| *S*-Carotene-5,6-epoxide | Acetone extract/fruits | Giuffrida et al. (2013) |
| *S*-Cryptoxanthin-C12:0 | Acetone extract/fruits | Giuffrida et al. (2013) |
| *S*-Cryptoxanthin-C14:0 | Acetone extract/fruits | Giuffrida et al. (2013) |
| Violaxanthin | MeOH extract; MeOH:water extract/fruits | Deli et al. (2001); Marín et al. (2004); de Sá Mendes and de Andrade Gonçalves (2020) |
| Zeaxanthin | MeOH extract/; MeOH:water extract; acetone extract/fruits | Mouly et al. (1999); Deli et al. (2001); Marín et al. (2004); Giuffrida et al. (2013) |
| Zeaxanthin-C12:0 | Acetone extract/fruits | Giuffrida et al. (2013) |
| Zeaxanthin-C12:0, C12:0 | Acetone extract/fruits | Giuffrida et al. (2013) |
| Zeaxanthin-C14:0 | Acetone extract/fruits | Giuffrida et al. (2013) |
| Zeaxanthin-C14:0, C14:0 | Acetone extract/fruits | Giuffrida et al. (2013) |
| Zeaxanthin-C14:0, C16:0 | Acetone extract/fruits | Giuffrida et al. (2013) |
| $\alpha$-Carotene | MeOH extract; acetone extract/fruits | Deli et al. (2001); Cserháti (2006); Giuffrida et al. (2013) |
| $\alpha$-Cryptoxanthin | MeOH extract; acetone extract/fruits | Deli et al. (2001); Cserháti (2006); Giuffrida et al. (2013) |
| $\beta$-Carotene | MeOH:water extract; acetone extract; MeOH extract/fruits | Mouly et al. (1999); Marín et al. (2004); Giuffrida et al. (2013); Deli et al. (2001) |
| $\beta$-Cryptoxanthin | MeOH extract; MeOH:water extract/fruits | Mouly et al. (1999); Deli et al. (2001); Marín et al. (2004); Hallmann and Rembiałkowska (2012) |
| VIII. *Carbohydrates* | | |
| Arabinose | MeOH extract/fruits | Mudrić et al. (2017) |
| Fructose | MeOH extract/fruits | Mudrić et al. (2017) |
| Galactitol | MeOH extract/fruits | Mudrić et al. (2017) |
| Glucose | MeOH extract/fruits | Mudrić et al. (2017) |
| Maltose | MeOH extract/fruits | Mudrić et al. (2017) |
| Mannose | MeOH extract/fruits | Mudrić et al. (2017) |

**TABLE 1** (Continued)

| Phytochemicals | Extract/part used | References |
|---|---|---|
| Raffinose | MeOH extract/fruits | Mudrić et al. (2017) |
| Rhamnose | MeOH extract/fruits | Mudrić et al. (2017) |
| Ribose | MeOH extract/fruits | Mudrić et al. (2017) |
| Sorbitol | MeOH extract/fruits | Mudrić et al. (2017) |
| Sucrose | MeOH extract/fruits | Mudrić et al. (2017) |
| Trehalose | MeOH extract/fruits | Mudrić et al. (2017) |
| Xylose | MeOH extract/fruits | Mudrić et al. (2017) |
| IX. *Aroma-active volatile compounds* | | |
| (*E*)-2-Nonene-4-thio | Water extract/fruits | Naef et al. (2008) |
| (*E*)-3-Heptene-2-thiol | Water extract/fruits | Naef et al. (2008) |
| (*E*)-4-Heptene-2-thiol | Water extract/fruits | Naef et al. (2008) |
| (*E*)-4-Nonene-2-thiol | Water extract/fruits | Naef et al. (2008) |
| (*Z*)-4-Heptene-2-thiol | Water extract/fruits | Naef et al. (2008) |
| (*Z*)-4-Nonene-2-thiol | Water extract/fruits | Naef et al. (2008) |
| 1-(2-thienyl)-2-Pentanethiol | Water extract/fruits | Naef et al. (2008) |
| 1-Nonene-4-thiol | Water extract/fruits | Naef et al. (2008) |
| 2,4-Heptane-dithiol | Water extract/fruits | Naef et al. (2008) |
| 2,4-Nonane-dithio | Water extract/fruits | Naef et al. (2008) |
| 2-Mercapto-4-heptanol | Water extract/fruits | Naef et al. (2008) |
| 2-Mercapto-4-heptanone | Water extract/fruits | Naef et al. (2008) |
| 2-Methylthio-4-heptanethio | Water extract/fruits | Naef et al. (2008) |
| 2-Nonanethiol | Water extract/fruits | Naef et al. (2008) |
| 2-Pentylfuran | Water extract/fruits | Buttery, Seifert, Guadagni, and Ling (1969) |
| 3-Isobutyl-2-methylpyrazine | Water extract/fruits | Buttery et al. (1969) |
| 3-Methyl-5-pentyl-1,2-dithiolane | Water extract/fruits | Naef et al. (2008) |
| 3-Methyl-5-propyl-1,2-dithiolane | Water extract/fruits | Naef et al. (2008) |
| 4-Mercapto-2-heptanol | Water extract/fruits | Naef et al. (2008) |
| 4-Mercapto-2-heptanone | Water extract/fruits | Naef et al. (2008) |
| 4-Mercapto-2-nonanol | Water extract/fruits | Naef et al. (2008) |
| 4-Methylthio-2-heptanethio | Water extract/fruits | Naef et al. (2008) |
| 4-Methylthio-2-heptanethiol | Water extract/fruits | Naef et al. (2008) |
| 4-Nonanethiol | Water extract/fruits | Naef et al. (2008) |
| Benzaldehyde | Water extract/fruits | Buttery et al. (1969) |
| Deca-*trans*,*trans*-2,4-dien | Water extract/fruits | Buttery et al. (1969) |
| Furfural | Water extract/fruits | Buttery et al. (1969) |
| Heptan-2-one | Water extract/fruits | Buttery et al. (1969) |
| Hept-*trans*-3-en-2-one | Water extract/fruits | Buttery et al. (1969) |
| Hexane | Water extract/fruits | Buttery et al. (1969) |
| Hex-*cis*-3-eno | Water extract/fruits | Buttery et al. (1969) |
| Hex-*trans*-2-enal | Water extract/fruits | Buttery et al. (1969) |
| Limonene | Water extract/fruits | Buttery et al. (1969) |
| Linalool | Water extract/fruits | Buttery et al. (1969) |
| Methyl salicylate | Water extract/fruits | Buttery et al. (1969) |
| Non-1-en-4-one | Water extract/fruits | Buttery et al. (1969) |
| Nona-*trans*,*cis*-2,6-diena | Water extract/fruits | Buttery et al. (1969) |
| Nona-*trans*,*trans*-2,5-dien-4-one | Water extract/fruits | Buttery et al. (1969) |

(Continues)

**TABLE 1** (Continued)

| Phytochemicals | Extract/part used | References |
|---|---|---|
| Non-*trans*-2-en-4-one | Water extract/fruits | Buttery et al. (1969) |
| Phenylacetaldehyde | Water extract/fruits | Buttery et al. (1969) |
| X. *Others* | | |
| Capsidiol | MeOH extract/fruits | De Marino et al. (2006) |
| Inosine | MeOH extract/fruits | De Marino et al. (2006) |
| Loliolide | MeOH extract/fruits | De Marino et al. (2006) |
| Oxylipin | MeOH extract/fruits | De Marino et al. (2006) |
| Phosphatidylcholine | MeOH extract/fruits | De Marino et al. (2006) |
| Uridine | MeOH extract/fruits | De Marino et al. (2006) |

4-hydroxy-3-methoxybenzyl (*E*)-8-methyl-6-nonenoate, whereas the dihydrocapsiate was reported as 4-hydroxy-3-methoxybenzyl 8-methylnonanoate and the nordihydrocapsiate was reported as 4-hydroxy-3-methoxybenzyl 7-methyloctanoate (Kobata et al., 1998, 1999). The HPLC coupled with LC–MS analysis of the red bell pepper fruits extracts reported the presence of five major glycolipids including acylated steryl glucoside, monogalactosyldiacylglycerol, steryl glucoside, glucocerebroside (ceramide monoglucoside), and digalactosyldiacylglycerol (Yamauchi et al., 2001).

The hydroalcoholic extract of the ripe fruits of *C. annum* are also rich sources of a variety of bioactive carotenoids and apocarotenoids (Deli et al., 2001; Gregory et al., 1987; Maoka, Akimoto, Fujiwara, & Hashimoto, 2004; Marín et al., 2004; Mouly et al., 1999; Yamauchi et al., 2001). The different colorings in *C. annuum* fruits are due to the presence of a high amount of carotenoids (de Sá Mendes & de Andrade Gonçalves, 2020). The HPLC analysis of the methanolic extract of *C. annuum* fruits reported the presence of 34 carotenoids (Deli et al., 2001). The total carotenoid content in red ripe fruits was estimated at about 1.3 g/100 g of dry weight (Deli et al., 2001). It is reported that capsanthin (**29**) is the major carotenoid present in the fruits of *C. annuum* with accounted for 60% of the total carotenoids followed by $\beta$-carotene (**27**), zeaxanthin (**30**), cucurbitaxanthin A (**31**), and capsorubin (**32**) (Figure 5; Deli et al., 2001; Giuffrida et al., 2013; Gregory et al., 1987; Yamauchi et al., 2001). The other important carotenoids in the fruits of *C. annuum* included capsanthin 5,6-epoxide, capsanthin 3,6-epoxide, 5,6-diepikarpoxanthin, violaxanthin, antheraxanthin, $\beta$-cryptoxanthin, and various *cis* isomers and furanoid oxides (Cserháti, 2006; Deli et al., 2001; Maoka et al., 2004; Villa-Rivera & Ochoa-Alejo, 2020). Maoka et al. reported two new carotenoids namely 3′-deoxycapsanthin and 3,4-didehydroxy-3′-deoxycapsanthin from the methanolic extract of ripe fruits of *C. annum* (Maoka et al., 2004). The phytochemical analysis of the methanolic extract of ripe fruits of *C. annum* reported the presence of five new apocarotenoids such as apo-14′-zeaxanthinal, apo-13-zeaxanthinone, apo-12′-capsorubinal, apo-8′-capsorubinal, and 9,9′-diapo-10,9′-retro-carotene-9,9′-dione along with six others known apocarotenoids included as apo-8′-zeaxanthinal, apo-10′-zeaxanthinal, apo-12′-zeaxanthinal, apo-15-zeaxanthinal, apo-11-zeaxanthinal, and apo-9-zeaxanthinone (Maoka, Fujiwara, Hashimoto, & Akimoto, 2001). Some bioactive ester of carotenoids is also present in the methanolic fruits extract of *C. annuum* including capsanthin 3′-ester, capsanthin 3,3′-diester, capsorbin diester, and cucurbitaxanthin A-3′ester (Maoka, Mochida, et al., 2001). The major bioactive carotenoids in the fruits of *C. annuum* included capsanthin (**29**), capsanthin 3′-ester (**33**), and capsanthin 3,3′-diester (**34**) (Figure 5; Maoka, Mochida, et al., 2001; Mohd Hassan, Yusof, Yahaya, Mohd Rozali, & Othman, 2019).

The fruit compositions of *C. annuum* depend on the different maturity stages. The GC–MS analysis of *n*-hexane and chloroform fractions of the fruits of *C. annuum* reported the presence of various lipophilic and phenolic compounds and the levels of these compounds were varying on the different maturity stages (Conforti, Statti, & Menichini, 2007). It is reported that the hydroalcoholic extract (methanol:water; 70:30) of immature green *C. annuum* contains the highest amount of polyphenols, whereas the red ripe fruits had the highest content of vitamin C and provitamin A (Marín et al., 2004). Oboh and Rocha (2007) reported that the fruits of *C. annuum* contained 83.7% free soluble polyphenol and 16.3% bound polyphenols. The chemical comparison between the green and red fruits of peppers showed that the total soluble solid, acidity, fat, ash, protein and ascorbic acid contents were very high in red fruits, whereas the calcium and sodium contents were high only in green fruits. Potassium is the major mineral present in both green and red fruits of *C. annuum*. The content of zinc, manganese, and copper was similar in both green and red fruits of *C. annuum* (Martínez, Curros, Bermúdez, Carballo, & Franco, 2007).

The fruits of *C. annuum* contain several volatile components (Buttery et al., 1969). The major bioactive volatile components in the fruits of *C. annum* included 3-isobutyl-2-methoxy pyrazine (**35**), *trans*-$\beta$-ocimene (**36**), limonene (**37**), methyl salicylate (**38**), linalool (**39**), nona-*trans*, *cis*-2,6-dienal (**40**), deca-*trans*,*trans*-2,4-dienal (**41**), and hex-*cis*-3-enol (**42**) (Figure 6; Idrees, Hanif, Ayub, Hanif, & Ansari, 2020). The aqueous extract of the fruits of *C. annuum* also contained several new and known sulphur-containing volatile constituents (Naef et al., 2008). The GC coupled with MS analysis of the commercial hot and sweet *C. annuum* of Spanish revealed the presence of various volatile constituents which belonged to the chemical classes of phenols, aldehydes, ketones, alcohols, acids, esters, ethers, lactones, nitrogenous compounds, aromatic hydrocarbons, and alkanes (Mateo, Aguirrezábal, Domínguez, & Zumalacárregui, 1997). It

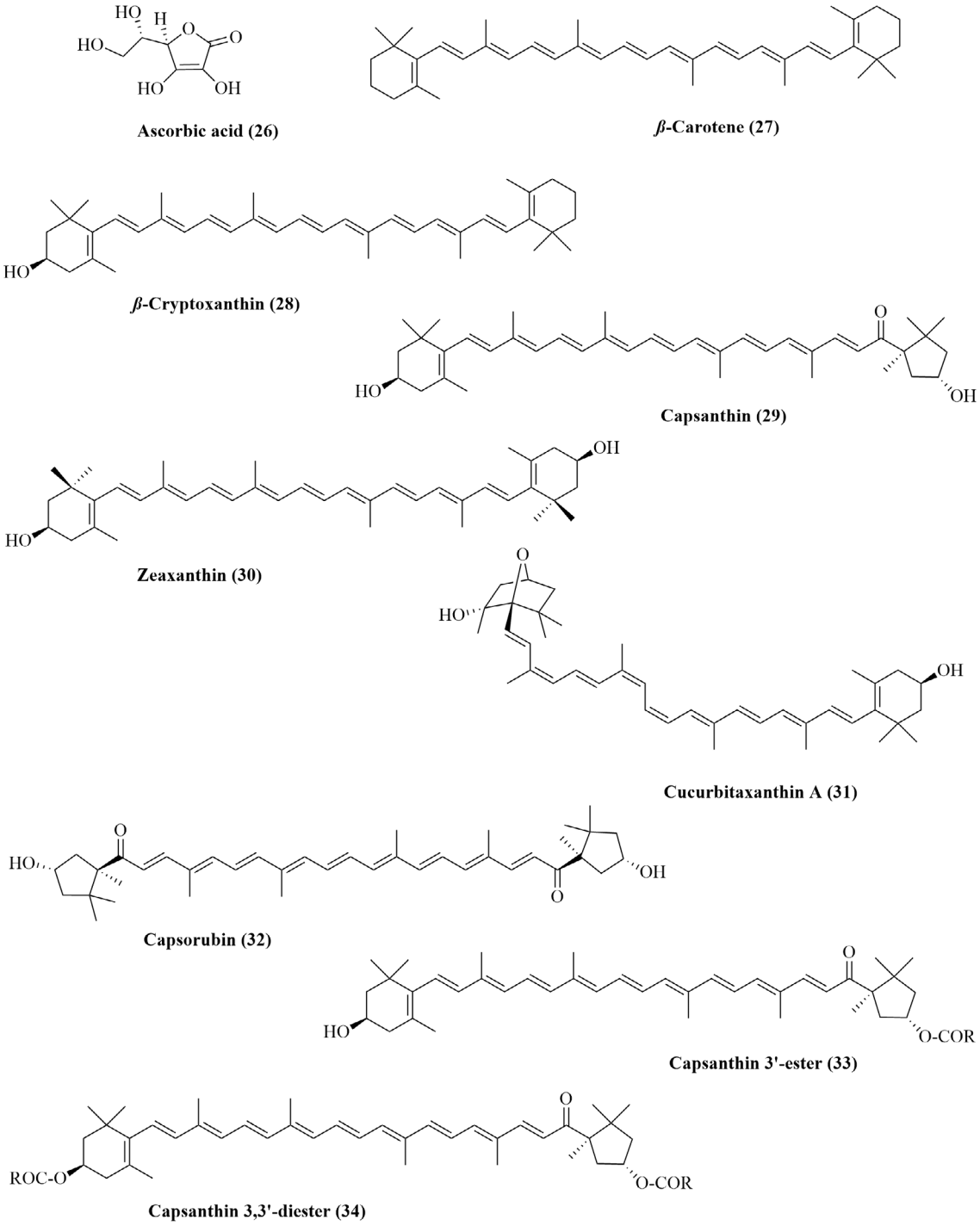


**FIGURE 5** Chemical structures of major vitamin C, provitamin A, and carotenoid constituents are present in the fruits of *C. annuum* L.

is reported that acetic acid (**43**) is the major volatile component in hot and sweet *C. annuum* followed by 1,3-butanediol (**44**), 2,3-butanediol (**45**), acetoin (**46**), 3-methylbutanal (**47**), ethyl acetate (**48**), and 2,6-dimethoxyphenol (**49**) (Figure 6; Mateo et al., 1997). The flavor of the fruits of *C. annuum* is due to the presence of several volatile compounds such as acetic acid, phenols, ethyl acetate, methyl branched aldehydes and acids, and other carbonyl compounds (Mateo et al., 1997).

As per the data available from United States Department of Agriculture Food Data Central (https://fdc.nal.usda.gov/fdc-app.html#/food-details/170106/nutrients, FDC ID: 170106 NDB Number:11819), the red fruits of *C. annuum* contain several vitamins to a level of

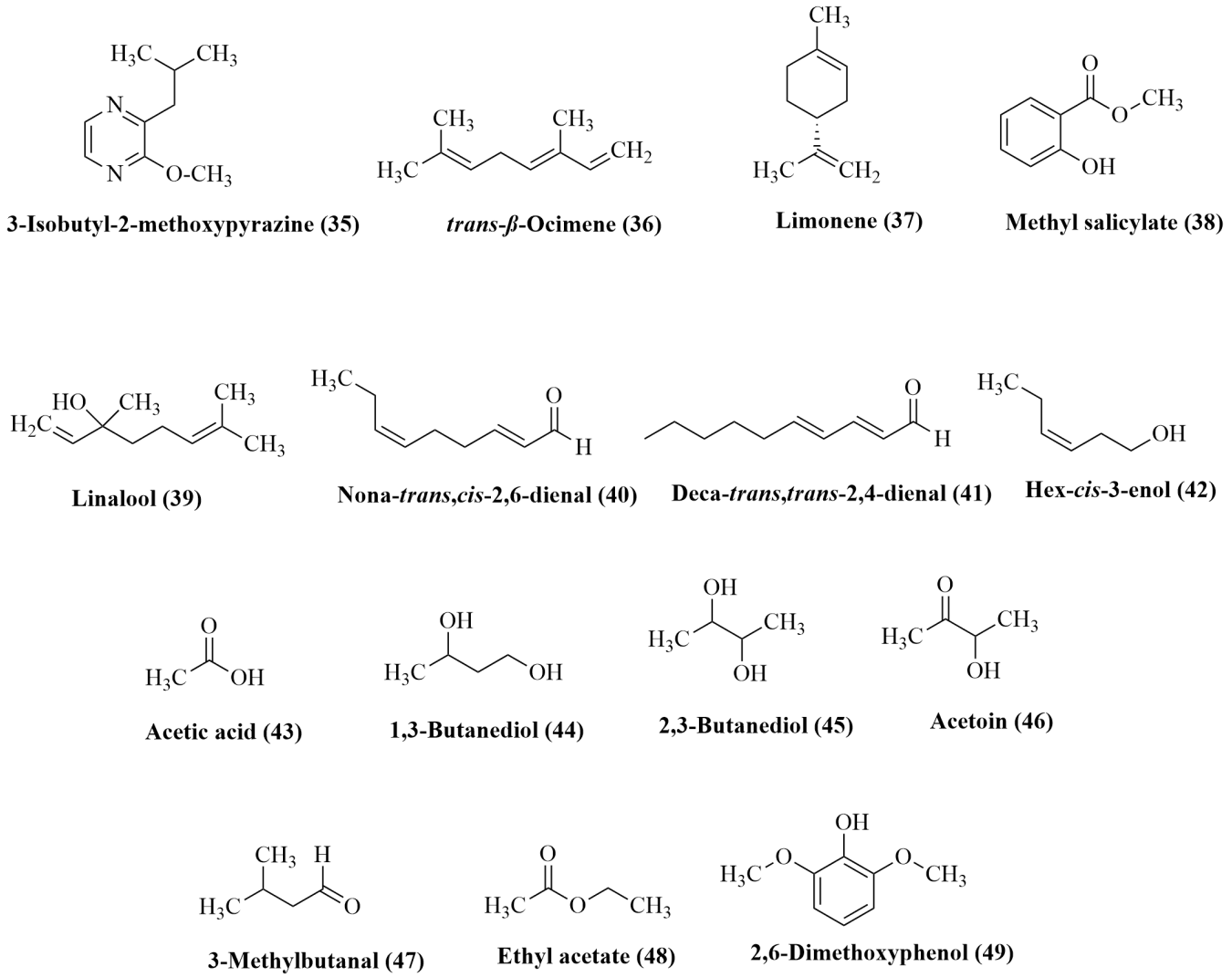


**FIGURE 6** Chemical structures of major bioactive volatile components present in the fruits of *C. annuum* L.

144 mg of ascorbic acid, 0.072 mg of thiamin, 0.086 mg of riboflavin, 1.24 mg of niacin, 0.201 mg of pantothenic acid, 0.506 mg of vitamin B-6, 23 mg of total folate, 10.9 mg of total choline, 48 mg of vitamin A (RAE, retinol activity equivalents), 534 mg of $\beta$-carotene, 36 mg of $\alpha$-carotene, 40 mg of $\beta$-cryptoxanthin, 952 IU of vitamin A, 709 mg of lutein and zeaxanthin, 0.69 mg of vitamin E ($\alpha$-tocopherol), and 14 μg of vitamin K (phylloquinone), per 100 g of red fruits. The red fruits of *C. annuum* also contain several minerals such as 14 mg of calcium, 1.03 mg of iron, 23 mg of magnesium, 43 mg of phosphorus, 322 mg of potassium, 3 mg of sodium, 0.26 mg of zinc, 0.129 mg of copper, 0.187 mg of manganese, and 0.5 μg of selenium, per 100 g of red fruits. The red fruits of *C. annuum* are also rich in several macronutrients such as 88 g of water, 40 kcal of energy, 1.87 g of protein, 0.44 g of total lipid, 0.87 g of ash, 8.81 g of carbohydrate, 1.5 g of total dietary fiber, and 5.3 g of total sugars, per 100 g of red fruits. The red fruits of *C. annuum* are also rich sources of several important essential as well as non-essential amino acids. The 100 g of red fruit contains 0.026 g of tryptophan, 0.074 g of threonine, 0.065 g of isoleucine, 0.105 g of leucine, 0.089 g of lysine, 0.024 g of methionine, 0.038 g of cysteine, 0.062 g of phenylalanine, 0.042 g of tyrosine, 0.084 g of valine, 0.096 g of arginine, 0.041 g of histidine, 0.082 g of alanine, 0.286 g of aspartic acid, 0.264 g of glutamic acid, 0.074 g of glycine, 0.087 g of proline, and 0.08 g of serine. The 100 g of red fruits also contained 0.042 g of total saturated fatty acids, 0.024 g of total monounsaturated fatty acids, and 0.239 g of total polyunsaturated fatty acids.

The phytochemical analysis of the methanolic extract of dried seeds of *C. annuum* reported the presence of three new significant antimicrobial furostanol saponin glycosides namely capsicoside E, capsicoside F, and capsicoside G along with seven other known oligo-glycosides (Iorizzi et al., 2002; Svobodová & Kuban, 2018). Yahara and his co-workers (1994) identified four new steroidal glycosides namely capsicosides A, B, C, and D with proto-degalactotigonin from the methanolic extract of roots and seeds of *C. annuum*. The 100 g of red pepper seeds were reported to contain 7.4 g water, 16.1 g protein, 1.8 g fat, 71.3 g carbohydrate, 35.0 g fiber, 3.4 g ash, 57 mg Ca, 466 mg P, 7.0 mg Fe, 0.64 mg thiamine, 0.29 mg riboflavin, 11.8 mg niacin, and 29 mg ascorbic acid (Duke, 1993). The nutritive values of dried Indian chilies per 100 g of edible portion were reported to

contain protein 15.9 g, fat 6.2 g, minerals 6.1 g, fiber 30.6 g, carbohydrates 31.6 g, phosphorus 370 mg, Ca 160 mg, Fe 0.0023 mg, carotene 345 μg, and ascorbic acid 50 mg (Krishna, 2021). The mineral content of the fruits of *C. annuum* depends on the different maturity stages. The red pepper contained a higher level of K, Mg, P, Fe, Cu, Zn, Mn, and B than the green pepper (Guilherme, Reboredo, Guerra, Ressurreição, & Alvarenga, 2020).

## 4 | USES OF *C. annuum*

### 4.1 | Traditional uses

Since ancient times, chili has been used as a culinary spice and is known for a number of therapeutic properties. *C. annuum* fruits are mainly used as flavoring agents. In the medicinal system, it is used as a tonic, antiseptic, rubefacient, and stimulating agent (T. Lim, 2013; Peter & Babu, 2012). The fruits are used externally and internally for the treatment of various diseases. The fruit part is used as a condiment and is given internally as a powerful stimulant, carminative, and also in flatulent dyspepsia (Qasem, 2020). The fruits boiled along with coconut oil, showed treating effects when added to the ears for the treatment of earache in traditional remedial medicine (Rajan & Sethuraman, 2008). Externally, it is used as a local stimulant, counter-irritant, and rubefacient, and for the treatment of rheumatism, lumbago, neuralgia, and varicose veins (Khare, 2004; Qasem, 2020). The cream containing 0.025% or 0.075% capsaicin is topically useful in pain disorders, neuropathy, cluster headache, migraine, psoriasis, trigeminal neuralgia, and herpes zoster (Khare, 2004). Internally, it is used to treat hoarseness, atonic dyspepsia, loss of appetite, flatulence, atherosclerosis, stroke, heart diseases, and muscle tension (Khare, 2004; Qasem, 2020). The tincture of fruits with other herbal supplements is used for lethargic affections, atonic gout, cholera, and sore throat. The tinctures of *Capsicum* are added to gargles for pharyngitis and sore throat. Its ointment is applied to painful joints in rheumatoid arthritis (Kunnumakkara et al., 2009). In the Unani medicine system, it is used to prevent cold, sinus infection, sore throat, spermaturia, prostate catarrh, digestion, and to increase blood flow (Khare, 2004). It is also used to improve digestion and circulation, prevent bleeding from ulcers, and prevent cold, sinus infection, and sore throat (Batiha et al., 2020). In folk medicine, fruits are used for cancer or tumors, asthma, and cough. Also, the regular ingestion of red fruit was shown beneficial for the treatment of anorexia, hemorrhoids, liver congestion, and varicose veins (Duke, 1993; Huang, Xue, Jiang, & Zhu, 2013; Maji & Banerji, 2016). It is been reported for traditional use against common cold, dyspepsia, and diarrhea, and applied as a blood purifier, laxative, and aphrodisiac (Hamayun, 2007).

### 4.2 | Non-medicinal traditional uses

The fruits of *C. annuum* are used as spices worldwide for their pungent test and flavor. The green and red fruits singly or with other vegetables are used eaten as a vegetable. This spice vegetable is very much familiar to the cuisine in making food, sausage, salads, pickles, and meat preparation (Farooqi et al., 2005; Hernández-Pérez et al., 2020). In Morocco, Europe, and California the fruits are used as natural coloring agents for vegetables. The chilhuacle chili provides unique flavor characteristics in Mexico and is used as an ingredient in cuisine (García-Gaytán, Gómez-Merino, Trejo-Téllez, Baca-Castillo, & García-Morales, 2017). In Pakistan, it has been used as a flavoring agent, condiment, stimulant, spices, and in salads, and also used in pickles (Hamayun, 2007).

## 5 | PHARMACOLOGICAL ACTIVITIES OF *C. annuum* AND ITS ACTIVE CONSTITUENTS

### 5.1 | Antibacterial activity

The ethanol solution extract of *C. annuum* fruit showed potential antibacterial activity against Gram-positive and Gram-negative bacteria as expressed in minimum inhibitory concentration (MIC) values. The 10 μl fruit extract in DMSO at the desired concentration showed inhibitory activity against *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Bacillus subtilis*, and *Sarcina lutea* (Hosseini, Djahaniani, & Nabati, 2021). The ethyl acetate extract of endophytic fungus *Paraconiothyrium brasiliense* from the fruit of *C. annuum* was observed rich source of flavonoid (31.53 ± 0.9 mg of QE/g of extract) and phenolic (2.59 ± 0.06 mg of GAE/g of extract). Further investigation also reported that the ethyl acetate extract acts as a great source of antimicrobial agents and has shown significant equipotent bacterial inhibitory activity like tetracycline hydrochloride. The same has also shown antioxidant and anticancer activity against prostate cancer (PC3) cell lines (Sathiyaseelan, Saravanakumar, Mariadoss, Kim, & Wang, 2021). Samrot, Shobana, and Jenna (2018) evaluated the antibacterial and antioxidant activities of different phytochemical compounds. Three stages of ripened fruit (green, yellow, and red) of *C. annuum* were extracted and the aqueous extract of yellow fruit showed the highest antibacterial activity against *P. aeruginosa*. A nanoparticulate preparation of green fruits showed the highest bactericidal activity against *P. aeruginosa* when tested by protein leakage assay method where water was used as negative control and ciprofloxacin (8 μg) was used as a positive control (Samrot et al., 2018). The methanolic extract of *C. annuum* fruits was identified to show antibacterial activity with MIC ranging between 64 and 2048 μg/ml against infected wounds in *S. aureus 18* (ATCC25923) and *E. coli 64R* (ATCC9739) (Ekom, Tamokou, & Kuete, 2021). The ethanol solution extract of *C. annuum* fruits was used for Carbopol-based formulation containing capsaicin where the release of the capsaicin was 50% within 52 hr. Moreover, the in vitro drug release study of the same via dialyzes membrane method and the capsaicin and Carbopol formulation showed significant antimicrobial activity at a concentration range of 0.312–10 μg/ml against a wide variety of bacterial strains namely *E. coli* (ATCC 10536), *Bacillus cereus* (Peru MycA 4), *Salmonella typhi* (Peru Myc 7), *S. aureus* (ATCC 6538); *Candida tropicalis* (YEPGA 6184), *Candida albicans* (YEPGA 6379), *Candida parapsilosis*

(YEPG 6551) *C. albicans* (YEPG 6138), *C. parapsilosis* (ATCC 22019), and *Candida krusei* (ATCC 6258) (Goci et al., 2021). The ethanol solution extract of *C. annuum* showed a zone of inhibition (6.33 ± 0.58 mm) reflecting efficient antibacterial activity against *Streptococcus pneumoniae* (Ďúranová et al., 2021). Chemical investigation of *Capsicum* extract revealed that the capsaicin, capsidiol, oleoresins, *m*-coumaric acids, *t*-cinnamic acid, and its derivatives were responsible for the better antibacterial inhibitory activity against Gram-positive bacteria and Yeast but lower activity against Gram-negative bacteria. Different concentrations of nano-emulsions prepared using tween 80 and tetraethyl orthosilicate, have shown promising antimicrobial activities using the cup plate method. It was observed that these nano-emulsions have no toxic effect on the human cell lines. As per their report, the cotton fabric treated with low *Capsicum*-based nano-emulsion (2.5%) has shown notable antimicrobial properties and killed microbes even after 10 washing cycles (El-Naggar, Soliman, Morsy, & Abdel-Aziz, 2020; Rajamanickam & Nakkeeran, 2020). The inhibitory effect of capsaicin was observed in in vitro study that inhibited the growth of *Helicobacter pylori* and in in vivo study on infected male *Mongolian gerbils* which showed chemoprevention of *H. pylori* through modulation of TNF-α expression in the pyloric mucosa and activating the formation of phospho-IκB-α resulting in activation of NF-κB signaling pathway in gastric epithelial cells which was independent of direct antibacterial effects (Toyoda et al., 2015). The polyphenols and carotenoids present in the methanolic extract of *C. annuum* were also responsible for antibacterial activity against *B. cereus* and *E. coli* (Nazzaro et al., 2009). It has been reported that 200 μg/ml capsidiol showed bacteriostatic properties against *H. pylori* (De Marino et al., 2006). Koffi-Nevry, Kouassi, Nanga, Koussémon, and Loukou (2012) have carried out an antibacterial activity against *S. aureus*, *Salmonella typhimurium*, and *Vibrio cholerae* strains using unblemished fruits of aqueous and methanol extracts of *C. annuum*. The results on antibacterial activity for the aqueous and methanol extract showed a zone of inhibition ranging from 11 to 14 mm for the disc diffusion and from 11 to 21 mm for the good diffusion assay. The methanol extract showed a much lower MIC of 0.2 mg/ml for *C. annuum* indicating a strong antibacterial activity on *V. cholerae* a Gram-negative non-Enterobacteriaceae bacteria. The MIC value for the aqueous extract of *C. annuum* was 0.25 mg/ml on *V. cholerae* and 0.5 mg/ml for other bacterial strains. The MIC values of *C. annuum* ranged from 1 to 2.5 mg/ml where both extracts showed the same MICs but methanol extract showed greater bactericidal activities than the aqueous extract. The MIC values were ranging from 1–2 mg/ml on *V. cholerae*, whereas these values ranged from 2 to 2.5 mg/ml against *S. aureus* and *S. typhimurium* (Koffi-Nevry et al., 2012). Yamasaki et al. (2011) studied the antimicrobial activity of methanolic extract of red chili and the results showed to possess multi-drug resistant against *V. cholerae* strains. The inhibitory mechanism of active constituent capsaicin caused suppression in cholera toxin production in *V. cholerae* by reducing the expression of major virulence-related genes such as *ctxA*, *tcpA*, and *toxT* (Yamasaki et al., 2011).

## 5.2 | Antifungal activity

The peptide extraction from fractionated fruit extract of *C. annuum* showed potential antifungal activity by showing loss of viability at a range of 96.15 to 100% against *C. albicans* (da Silva Gebara et al., 2020). In a cation-exchange chromatographic analysis of seed extract, the peptide-rich F3 fraction showed inhibitory activity against *Saccharomyces cerevisiae*, *Candida parapsilosis*, *C. tropicalis*, *Pichia membranifaciens*, *Kluyveromyces marxiannus*, *C. albicans*, and *Candida guilliermondii* with $IC_{50}$ values (μg/ml) of >32, >64, >64, >16, 16, >16, and >16, respectively (Ribeiro et al., 2007). L. P. Cruz et al. (2010) studied the activity using extracts and isolated peptides from chili and reported their effect on various microbes including fungi.

## 5.3 | Antioxidant activity

The antioxidant activity of methanolic extract of various colored *C. annuum* fruits (green, yellow, orange, and red) evaluated using 2,2′-diphenyl-1-picrylhydrazyl (DPPH) method demonstrated interesting observations. All the fruit extracts showed the ability to prevent the oxidation of cholesterol by 71.3, 66.1, 62.0, and 84.4%, respectively (green, yellow, orange, and red colored fruits). The prevention ratio accounted for 67.8, 48.5, 56.6, and 53.1%, respectively (for green, yellow, orange, and red colored fruits) in docosahexaenoic acid (DHA) oxidation method. The red-colored fruits extract in the DPPH method and green-colored fruits extracts in the DHA method showed higher antioxidant activity (J.-H. Park, Jeon, Kim, & Park, 2012; Samrot et al., 2018; Sun et al., 2007). A study reported the presence of some water-soluble components in the fruit of *C. annuum* which led to antiradical and antioxidant properties when treated against pepper mild mottle virus infected. The study showed potent effects when compared to reference standard vitamin C content of infected fruits that were found significantly lower (Dikilitas, Guldur, Deryaoglu, & Ozcan, 2011). The antioxidant activity of Quercetin 3-*O*-α-L-rhamnopyranoside, quercetin 3-*O*-rhamnoside, luteolin-7-*O*-(2-apiosyl)-glucoside, capsaicin, and dihydrocapsaicin present in the fruits extract, using DPPH test and ß-carotene-linoleic acid system, showed potential antioxidant activity (Materska, Konopacka, Rogoliński, & Ślosarek, 2015; Sandoval-Castro et al., 2017). A new capsaicin derivative, 6′′,7′′-dihydro-5′,5′′′-dicapsaicin showed a strong antioxidant activity with an $IC_{50}$ value of 10 μM as compared to α-tocopherol with an $IC_{50}$ value of 250 μM (Ochi et al., 2003). Phytochemicals such as lycopene, ascorbic acid, *p*-coumaryl alcohol, ethoxyquin, and capsaicinoids from *C. annuum* showed significant antioxidant activity (Idrees et al., 2020; Kuzukiran et al., 2018; Materska & Perucka, 2005). Oboh, Puntel, and Rocha (2007) studied the antioxidant activity on the isolated phytochemicals and showed potent activity against Fe(II)-induced lipid peroxidation in rat brain. They also reported the total phenol content of *C. annuum* seemed higher than the total phenol content reported in *C. chinese* (Oboh et al., 2007). J.-H. Park et al. (2012) studied the activity using methanolic extracts of four different

colored (red, orange, yellow, and green) fruits of *C. annuum* and demonstrated a higher level of total phenolic content in red and orange bell peppers. However, orange bell pepper has shown the highest antioxidant activity of all. Whereas, all the colored extracts of bell peppers have shown significant activity by inhibiting 4-hydroxy-2-nonenal-induced and $H_2O_2$-induced DNA damage in human leukocytes. Additionally, these extracts could induce cell death in human colorectal cancer cells HT-29 by decreasing cell proliferation and increasing lactate dehydrogenase (LDH) release (J.-H. Park et al., 2012). The antioxidant levels of capsaicin showed an inhibitory effect on lipid peroxidation in rat liver (Kursunluoglu, Taskiran, & Ayar Kayali, 2018). The recent report suggested the effects of capsaicin as an ovarian antioxidant which showed increased plasma glutathione peroxidase activity, resulting in improved egg production, and follicular development in aged laying ducks by activating the calcium signaling pathway (J. Liu, Xia, et al., 2021).

Capsaicin showed significant in vivo antioxidant effects protective against oxidative stress on erythrocytes of male Wistar rats by elevating FRAP, GSH level, and PMRS activity through sensory neurons via transient receptor potential vanilloid 1 (TRPV1) activation (Chaudhary, Gour, & Rizvi, 2022). The antioxidant effect of both capsaicin and $\alpha$-tocopherol was studied on mitochondrial function in the liver of mice fed high-fat diet, which resulted in the elevation of oxidative stress parameters and significant inhibition of lipid peroxidation with improved ameliorative effect when both were co-administered (Şekeroğlu, Aydın, Şekeroğlu, & Kömpe, 2018). Curcumin and capsaicin individually reduced the nonspecific elevation of serum liver function enzymes and act as protective against lipopolysaccharide (LPS)-induced hepatotoxicity in mice. However, when both were co-administered the beneficial effect was observed more by reducing the release of SGOT, SGPT, ALP, LDH, and alkaline phosphatase (AP) into the blood stream (Vasanthkumar, Hanumanthappa, Prabhakar, & Hanumanthappa, 2017).

## 5.4 | Immunomodulatory activity

The ethanol solution extract of fruits and capsaicin, both showed immunomodulatory activity in ex vivo and in vitro on murine Peyer's patch (PP) cells. The extract and capsaicin modulated T cells (T helper 1 and 2) responses via TRPV1-dependent and -independent pathways. In vitro direct administration of ethanol extract (1 and 10 μg/ml) and capsaicin (3 and 30 μM) suppressed the production of interleukin-2 (IL-2), interferon- γ (IFN-γ), IL-4, and IL-5 on murine PP cells. In ex vivo oral administration of *Capsicum* extract (10 mg/kg/day) increased the production of IL-2, IFN-γ, and IL-5 reduced the population of $CD3^+$ and increased the $CD19^+$ cells. Oral administration of capsaicin (3 mg/kg/day) also increased the production of IL-2, IFN-γ, and IL-4 in response to the concanavalin A on PP cells. But the oral administration of extract and capsaicin did not alter the ratio of T cell subset $CD4^+$/$CD8^+$, Th1/IFN-γ, and T2/IL-$4^+$ (Takano et al., 2007). Capsicum extract and its constituents, mainly capsaicin and carotenoids, could considerably elevate the production of immunoglobulins in PP cells by decreasing the production of antibodies by increasing the number of $CD19^+$ B cells and a decrease in $CD3^+$ T cells in PP cells, thus helping enhancement of intestinal humoral immune responses via antibody secretion, whereas carotenoids could not show the effects (Yamaguchi, Yahagi, Kato, Takano, & Ohta, 2010).

## 5.5 | Anticancer activity

Several reports demonstrate that capsaicin has anticancer activity against a variety of cancers including bladder cancers (Baenas, Belović, Ilic, Moreno, & García-Viguera, 2019), malignant human glioblastoma (Adami et al., 2018), melanoma (M.-H. Liu, Li, & Chen, 2021), esophagus epidermoid carcinoma (Khandel, Yadaw, Soni, Kanwar, & Shahi, 2018), human oral tumor (H.-G. Kim et al., 2016), gastric adenocarcinoma (H.-G. Kim et al., 2016), and prostate cancer (Chilczuk et al., 2020). Capsaicin inhibited the growth of human colon cancer by inducing apoptosis and G0/G1 phase cell cycle arrest (Jin et al., 2014). It induced apoptotic signaling through the release of cytochrome c and a decrease in the expression of Bcl-2 protein leading to activation of caspase-3. It also reduced the level of reactive oxygen species (ROS) and lipid peroxidation (K.-S. Chen et al., 2015). In melanoma cells, capsaicin-induced apoptosis through intracellular calcium entry through TRPV1 causes nuclear condensation and internucleosomal DNA fragmentation in a TRPV1-apoptosis pathway (Zhai, Liskova, Kubatka, & Büsselberg, 2020). The molecular mechanism of capsaicin was mediated through molecular-like targets tNOX (ENOX2) which induced apoptosis in human esophagus epidermoid carcinoma cells. It also caused cell cycle arrest at the G0–G1 phase by increased production of p53 and p21 caused inhibition of cyclin-dependent kinase-2 (Cdk2) and cyclin E complex (Islam, Su, Zeng, Chueh, & Lin, 2019). Capsaicin showed antiproliferative activity against prostate cancer cells and induced apoptosis in both androgen receptor (AR) positive (LNCaP) and AR-negative (PC-3, DU-145) prostate cancer cell lines (Díaz-Laviada & Rodríguez-Henche, 2014; Pecze et al., 2016). Capsaicin at a concentration range of 100–500 μM potently inhibited the growth and induced apoptosis in prostate cancer cell lines LNCaP, PC-3, and DU-145. Capsaicin at 500 μM concentration-induced apoptosis by 75% in PC-3 cells and 93% in LNCaP cells (Mori et al., 2006). Capsaicin treatment in Swiss albino mice lung tumor model showed apoptosis activity by increasing the expression of Bcl-2 protein suggesting that Bcl-2 may play an important role in capsaicin-induced apoptosis. It also modulated the expression of apoptosis-related proteins like p53, Bcl-2, Bax, and caspase-3 (Anandakumar, Kamaraj, Jagan, Ramakrishnan, & Devaki, 2013). The treatment of capsaicin in anaplastic thyroid carcinoma cells activated TRPV1 by modulating rapidly cytosolic $Ca^{2+}$ concentration causing mitochondrial calcium overload leading to the mitochondrial dysfunction and depolarization of membrane potential that leads to the release of cytochrome c into the cytosol and subsequent caspase activation and apoptosis (Xu et al., 2020).

*Capsicum* fruits are a rich sources of capsanthin, a xanthophyll class of carotenoids, which showed inhibitory activity against N-methylnitrosourea-induced colon carcinogenesis in F344 rats. *Capsicum* fruits extract containing 2 ppm capsanthin reduced the incidence of *N*-methylnitrosourea-induced colon cancer by 40% (Kennedy et al., 2021). Capsaicinoids and capsaicin mimetics capsanthin and related carotenoids like capsorubin diester, capsanthin 3′-ester, capsanthin 3,3′-diester, and capsanthin 3,6-epoxide in the fruit extract showed potential in vitro antitumor-promoting activity (Batiha et al., 2020). The topical capsaicin dose (0.42 mM) lowered the incidences of vinyl carbamate-induced skin tumors by 62% (Mózsik et al., 2014). Capsaicin isolated from *C. annuum* showed significant cell growth inhibition in both in vitro and in vivo models by altering the histone acetylation as well as reduced hMOF activity in gastric cancer cells (F. Wang et al., 2016). The significant activity of various flavonoids and capsaicinoids content in Mexican *C. annuum* has been observed for protective measures against oxidative damage in cancer cells (Vera-Guzmán et al., 2017).

Capsaicin and its synthetic derivative capsaicin epoxides were reported as a potential cytotoxic against MCF7 breast cancer cell lines at a concentration of 5 μM. However, capsaicin epoxide was found more effective and caused apoptotic cell death through multiple caspase pathways against hydrogen peroxide and *tert*-butyl hydroperoxide (*t*BuOOH). Whereas, capsaicin and capsaicin epoxide caused elevation in the intracellular ROS production to about 44 and 98% as compared to the control (Lewinska, Chochrek, Smolag, Rawska, & Wnuk, 2015). Anandakumar et al. (2012) studied the anticancer effects of capsaicin at 10 mg/kg body weight and showed that it inhibited the benzo(α)pyrene-induced lung microsomal monooxygenases involved in carcinogen activation that implies its antitumor activity in vivo. S.-H. Lee, Krisanapun, and Baek (2010) reported that capsaicin inhibited the growth of human lung cancer and colorectal cancer cells by up-regulating the *NAG-1* gene expression and binding of C/EBP$\beta$ with glycogen synthase kinase 3$\beta$ (GSK3$\beta$), and thus activated the transcription factor 3 (ATF3) and helped in inhibition of the GSK3$\beta$ and Protein Kinase C pathways. Capsaicin and its derivative hydroxycapsaicin were observed for potential cytotoxic histone deacetylase inhibitory activity by inducing S-phase cell cycle arrest in both HT29 and HCT116 colon cancer cells (Senawong, Wongphakham, Saiwichai, Phaosiri, & Kumboonma, 2015). The carotenoids namely capsanthin, capsanthin 3′-ester, capsanthin 3,3′-diester, capsorubin, capsorbin diester, capsanthin 3,6-epoxide, and cucurbitaxanthin A-3′ester exhibited significant in vitro antitumor activity on Epstein–Barr virus early antigen (EBV-EA) activation induced by 12-*O*-tetradecanoylphorbol-13-acetate (TPA) as a tumor promoter. Out of that carotenoids namely capsanthin, capsanthin 3′-ester, and capsanthin 3,3′-diester exhibited potent in vivo antitumor-promoting activity by mouse skin two-stage carcinogenesis assay through 7,12-dimethylbenz[α]anthracene as an initiator and TPA as a promoter (Maoka, Mochida, et al., 2001).

The anticancer potentials of *C. annuum* and capsaicin are summarized in Figure 7. It is proposed that the *C. annuum* as well as capsaicin is supposed to interact through the TRPV1 receptor and induce several intracellular signaling pathways leading to apoptosis as a

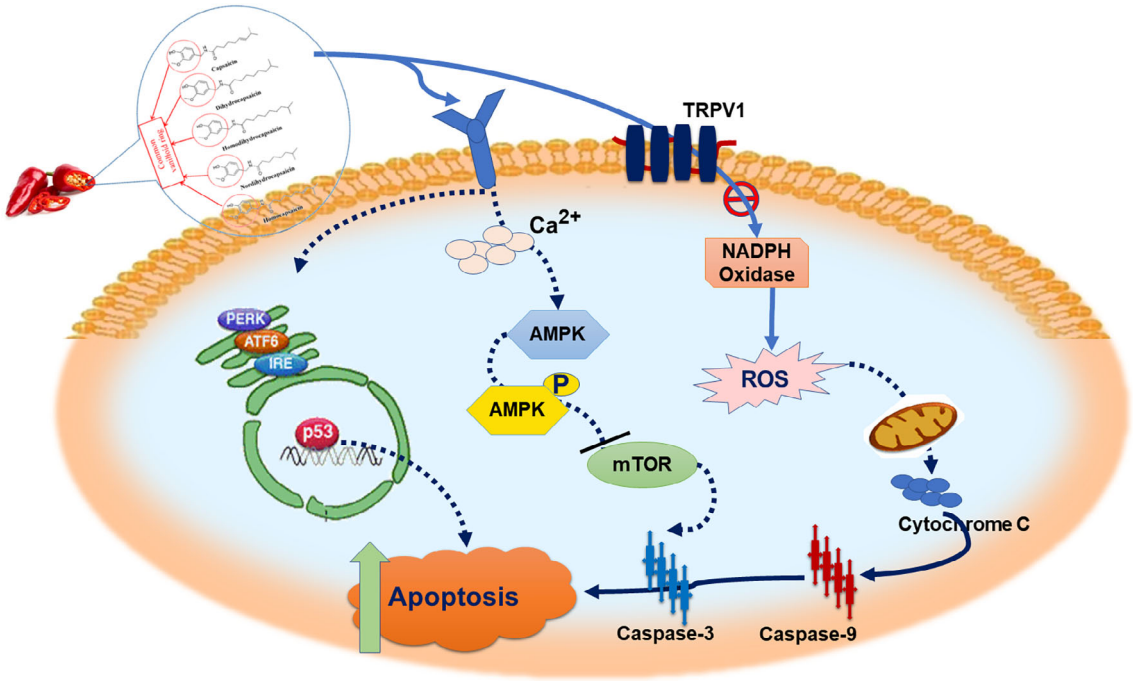


**FIGURE 7** The anticancer potentials of *C. annuum* L. and capsaicin are summarized in this figure. The mechanism of anticancer potential of *C. annuum* as well as capsaicin is proposed to interact through the TRPV1 receptor and induce several intracellular signaling pathways leading to apoptosis. It blocks the activity of NAPDH oxidase and triggers apoptosis through mitochondria, as well as leads to activation of p53 expression that too induces apoptosis reactivation. Whereas, it activated AMPK phosphorylation and thus inhibition of mTOR signaling that leads to apoptosis via capspase-3 cascade

mechanism of anticancer effect. It blocks the activity of NAPDH oxidase and triggers apoptosis through mitochondria, as well as leads to activation of p53 expression that mediates apoptosis reactivation. Whereas, it activated AMPK phosphorylation and thus inhibition of mTOR signaling that led to apoptosis via caspase-3 cascade.

## 5.6 | Antimutagenic activity

Several researchers have conducted the mutagenicity activity using the extract of *C. annuum* fruit extract which showed potential antimutagenic or anticarcinogenic responses (K. Srinivasan, 2017). In *Drosophila melanogaster* wing, 5 and 10% water extract of *C. annuum* produced a sharp reduction in the frequency of twin spots development, by 27 and 33% respectively, in methyl methanesulfonate-induced mutagenesis; and 30 and 43% activity in ethyl carbamate-induced mutagenesis as analyzed in somatic mutation and recombination test (El Hamss, Idaomar, Alonso-Moraga, & Serrano, 2003). The antimutagenicity or carcinogenicity effect of fruits extract was due to the presence of capsaicin, tannic acid, vitamin A, and carotenoids like *ß*-carotene (Batiha et al., 2020; de Mejía, Quintanar-Hernández, & Loarca-Piña, 1998; El Hamss et al., 2003). de Mejia and co-workers (1998) demonstrated the antimutagenic activity of pure *ß*-carotene and carotenoids-rich extract. The carotenoids-rich extract at a dose of 1.53 g inhibited the mutagenic effect of 1-nitropyrene, 1,6-dinitropyrene, and 1,8-dinitropyrene by 87, 79, and 73%, respectively, in *S. typhimurium* tester strain YG1024, whereas 50 nM pure *trans-ß*-carotene only produced 50% inhibition. Not only *ß*-carotene, other mutagenic carotenoids, and functional nutrients produced a synergistic effects for the antimutagenic activity of *Capsicum* extract (de Mejía et al., 1998). The anticarcinogenic and antimutagenic effects of capsaicin were mediated by interacting with microsomal cytochrome P450-dependent monooxygenases which helped in the detoxification of various carcinogens or mutagens or other toxic xenobiotics (Surh & Lee, 1995). A smaller dose of capsaicin showed no deleterious effects and altered carcinogen metabolism, DNA binding capacity mutagenicity, and tumorigenicity of chemical mutagens or carcinogens; whereas a high capsaicin dose was associated with necrosis, ulceration, and even carcinogenesis. Pure capsaicin at 0.42 mM dose inhibited the mutagenic effect of vinyl carbamate and *N*-nitrosodimethylamine in *S. typhimurium* TA100 strain by 50 and 42%, respectively (Surh et al., 1995). Even intraperitoneal administration of capsaicin also inhibited the chemically induced chromosomal aberrations and DNA strand breakages. It was reported that intraperitoneal administration of capsaicin at a dose of 1.6 mg/kg body weight did not produce any mutagenic effects in adult mice (Bley, Boorman, Mohammad, McKenzie, & Babbar, 2012).

## 5.7 | Antiplatelet activity

Capsaicin was reported to suppress bacterial growth in some strains and act as a potent inhibitor of platelet aggregation in the rat (C. Y. J. Lee, Kim, Yoon, & Lee, 2003; Sharma, Vij, & Sharma, 2013). In vitro study showed that capsaicin inhibited collagen and thrombin-induced platelet aggregation in rats and inhibited the collagen-induced platelet aggregation with an $IC_{50}$ value of 85 μg/ml. The inhibition of platelet aggregation was due to the inhibition of ATP release, lowered malondialdehyde (MDA) accumulation, and TXB2 formation by capsaicin. Capsaicin at 175 μg/ml inhibited platelet aggregation in the presence of indomethacin (50 μg/ml) or a combination of both via the ADP scavenger creatine phosphate/creatine phosphokinase (CP/CPK). It also reduced the RBC cell's hemolysis by hydrogen peroxide or hypertonicity which indicated the membrane-stabilizing property of capsaicin which might lead to the inactivation of phospholipase A2 (J.-P. Wang, Hsu, & Teng, 1984).

## 5.8 | Antiangiogenic activity

A study on natural capsaicin showed that it had antiangiogenic activity in vitro and in vivo assay systems. In vitro study on human umbilical vein endothelial cells showed that capsaicin inhibited vascular endothelial growth factor (VEGF)-induced cells proliferation by G1 phase cell cycle arrest of endothelial cells, mediated through inhibition of cyclin D1 expression or induction of a CDK inhibitor (p21) leading to DNA synthesis, chemotactic motility, and capillary-like tube formation of primary cultured human endothelial at a dose concentration 5 μM. In vivo studies showed that capsaicin also inhibited VEGF and tumor-induced angiogenesis. It could inhibit in vivo tumor-induced new blood vessel formation in the chick chorioallantoic membrane assay. The subcutaneous doses of 20 or 60 μg/ml capsaicin significantly inhibited the hemoglobin quantity by 2.4 g/dl in C57BL/6 mice in comparison to VEGF*induced hemoglobin quantity (8.5 g/dl) (Min et al., 2004).

## 5.9 | Cardiovascular activity

Capsaicin showed prolonged cardiac action potential in rat atrial muscle (Hooper et al., 2016). It was found that 10 μM capsaicin enhanced the action potential duration ($APD_{50}$) from 45 to 166 ms in isolated adult rat ventricular myocytes by the inhibition of neuronal three different $K^+$ currents. The action potential of capsaicin produced action potential prolonging activity in the heart (Castle, 1992). Toda, Usui, Nishino, and Fujiwara (1972) reported that intravenous injections of capsaicin (10–300 μg/kg) increased the mean systemic blood pressure in dogs whereas the same doses produced hypotension in rabbits (Toda et al., 1972). The hypertension was due to the action of capsaicin on peripheral vasculatures. Capsaicin caused a sustained increase in the tension of spiral strips of proximal, distal mesenteric arteries, proximal, and distal renal arteries which were dependent on the extracellular concentration of $Ca^{++}$ (Toda et al., 1972). Intravenous injection of capsaicin at a dose of 1 μg increased arterial blood pressure and heart rate in comparison to the initial fall in blood pressure and heart rate in male Wistar rats anesthetized with urethane (Chahl & Lynch, 1987).

## 5.10 | Antihyperlipidemic activity

The ability of the lipid peroxidation of *Capsicum* extract was due to free and bound polyphenols. It was reported that the free polyphenols of *Capsicum* extract were more potent inhibitors of lipid peroxidation than bound polyphenols. The study by Oboh et al. (2007) reported that *C. annuum* contained 83.7% free soluble polyphenol (218.2 mg/100 g) and 16.3% bound polyphenols (42.5 mg/100 g) which could inhibit the various pro-oxidant agents like $Fe^{2+}$, sodium nitroprusside and quinolinic acid which induced lipid peroxidation in brain and liver tissues. These polyphenols showed protective roles on the brain and the liver from lipid peroxidation by chelating Fe(II), scavenging OH, NO radicals, and inhibition of over-stimulation of *N*-methyl-D-aspartate receptor. It is known that Fe accumulation in the brain and storage in the liver can induce oxidative stress and thus leads to damage in the brain and liver. This can be reduced due to the chelating ability of polyphenol extracted from *C. annuum* with Fe and hence could inhibit Fe(II) induced lipid peroxidation in in vivo models of rat liver. Additionally, β-glycoside moiety in the phenolic compound can have ability to reduce the uptake of phenolic bindings in the brain and liver tissues that may reduce antioxidant activity (G Oboh et al., 2007).

Capsaicin and dihydrocapsaicin showed antihyperlipidemic effects as well. A study on two groups of turkeys revealed that dihydrocapsaicin administration at a dose 4 mg/animal/day significantly decreased the serum triglycerides, total cholesterol, LDL-cholesterol, VLDL-cholesterol, and increased HDL-cholesterol levels in the cholesterol-fed animals but the higher concentration of dihydrocapsaicin dose (8 mg/animal/day) significantly altered food consumption, body weight, dry weight of feces, and decreased serum triglyceride level (Negulesco et al., 1987). On the other hand, oral administration of capsaicin (0.014%) lowered the perirenal adipose tissue weight, level of serum triglyceride, and reduced the activity of glucose-6-phosphate dehydrogenase and adipose lipoprotein lipase (Kawada, Hagihara, & Iwai, 1986). The carotenes like $\beta$-carotene, acyl derivatives of capsanthin, and acyl derivatives of capsorubin inhibited LDL oxidation in vitro with probable lowering of the "atherogenic" LDL subfraction production in vivo. Incorporation of these carotenoids into the human plasma effectively lowered the oxidation of LDL, inhibited conjugated dienes formation from polyunsaturated fatty acid, and modulated autoxidation of cholesterol. Dietary capsaicin also contributed to genetic alteration in bacteria by enhancing glucose homeostasis through rising short-chain fatty acids, regulating gastrointestinal hormones, and inhibiting pro-inflammatory cytokines (Medvedeva, Andreenkov, Morozkin, Sergeeva, & Alu, M., 2003).

The influence of *Capsicum* and capsaicin on fat absorption in rats in choline-free high hydrogenated fat (40%) diet was studied which showed that 5% red pepper or 15 mg capsaicin in the diet significantly lowered the serum and liver cholesterol levels (Sambaiah, Satyanarayana, & Rao, 1978). M. Srinivasan, Sambaiah, Satyanarayana, and Rao (1980) have shown the effect of capsaicin at 1.5, 3, and 15 mg incorporated with 10% groundnut oil in diet which significantly reduced serum total cholesterol levels in rats. In another study, M. Srinivasan and Satyanarayana (1987) showed the effects of capsaicin at a very low concentration of 0.2 mg and the results showed a significant reduction of serum total cholesterol in both 10 and 30 mg fat-fed rats. The effects of capsaicin on rats administered at 50 mg/kg body weight of capsaicin or 0.5 g/kg/day of *Capsicum* fruit extract for 60 days showed a significant decrease in the triglycerides and phospholipids levels (Monsereenusorn, 1983). M. Srinivasan and Satyanarayana (1988) studied the effects of capsaicin at 0.15, 1.5, and 15 mg for a period of 1 week which showed to significantly increase the total and HDL cholesterol levels. Sambaiah and Satyanarayana (1980) have reported the hypocholesterolemic effects of treatment with a 1% cholesterol +5% red pepper diet and the results showed to decrease the serum cholesterol levels, whereas on treatment with capsaicin the liver cholesterol levels were decreased. Kempaiah and Srinivasan (2002) reported that capsaicin showed changes in membrane lipid profile in the erythrocytes in rats fed with an atherogenic high-cholesterol diet. This study utilized a combination of capsaicin with dietary curcumin and garlic to manage the lipid profile which was decreased by 10–14%. Gupta, Dixit, and Dobhal (2002) reported the effects of capsaicin on rodents using *Capsicum* oleoresin at a concentration of 75 mg/kg and the results showed a significant decrease in the level of serum and liver cholesterol and triglycerides. It also prevented the accumulation of cholesterol and triglycerides in the liver and increased fecal cholesterol and triglycerides excretion (Gupta et al., 2002).

A study by Liang and co-workers (2013) on in vivo artery functionality in hamsters showed that capsaicinoids caused a decrease in the plasma total cholesterol, increased lipoprotein profiles, and reduced the aortic plaque in high-cholesterol-fed situations. Further, dietary capsaicinoids could increase the endothelium-dependent relaxations and reduce the endothelium-dependent contractions and increase fecal cholesterol excretion. Hence, capsaicinoids achieved its cholesterol-lowering and vascular activity under normal physiological conditions. The dietary capsaicinoids at doses ranging from 0.010 to 0.30% showed no effect on cholesterol synthesis as no significant change was found in liver cholesterol concentration and plasma ratio of lathosterol/cholesterol, whereas capsaicinoids helped in decreasing cholesterol absorption. In addition, dietary capsaicinoids were monitored in up-regulating the gene expression of CYP7A1 in the bile acid synthesis pathway and could down-regulate the gene expression of liver LXRα which assisted 36–64% greater excretion of bile acids (Liang et al., 2013).

## 5.11 | Energy metabolic activity

Hot red pepper ingestion enhanced carbohydrate oxidation during exercise and rest (K. Lim et al., 1997). Capsaicin has also shown an important role in energy metabolism. In vivo study on rats revealed that intraperitoneal administration of capsaicin at 4 mg/kg increased the level of serum glucose and these responses were not altered by hexamethonium bromide and atropine sulfate treatment (Watanabe, Kawada, & Iwai, 1987). The enhancement of the energy metabolism

was due to the production of catecholamine from the adrenal medulla of rats via the activation of the central nervous system (K. Lim et al., 1997; Watanabe et al., 1987; Watanabe, Kawada, Kurosawa, Sato, & Iwai, 1988).

## 5.12 | Gastroprotective activity

*C. annuum* fruits and its principal pungent component capsaicin protected the gastrointestinal mucosa from various toxic chemicals such as ethanol, indomethacin, aspirin, and other stressors (Barbero et al., 2014; Bode & Dong, 2011). Chili powder (360 mg daily) and capsaicin (5 mg/kg body weight) reduced the gastric mucosal injury in response to hemorrhagic shock in anesthetized male Sprague–Dawley rats but the gastroprotective activity of capsaicin was permanently abolished at a dose concentration of 125 mg/kg body weight (Teng, Kang, Wee, & Lee, 1998). Capsaicin administered intragastrically (2–5 mg/kg), subcutaneously (2 mg/kg), and orally (1–30 mg/kg) showed a significant gastroprotective effect against ethanol-induced gastric mucosal injury in the in vivo rat model. The report also suggested that the smaller doses of capsaicin could restrict gastric mucosal bleeding induced by NSAIDs (both COX-1 and COX-2 inhibitors). However, the gastric mucosal protective effect could not be seen at higher doses of capsaicin (Mózsik et al., 2014; Takeuchi, Tachibana, Ueshima, Matsumoto, & Okabe, 1992). The intragastrical administration of capsaicin inhibited lipid peroxidation, expression of COX-2, and myeloperoxidase enzyme activity in the ethanol-induced gastric mucosal lesion in Sprague–Dawley rats (J.-S. Park et al., 2000). Capsaicin was reported to protect the gastric mucosa via inhibition of gastric mortality, increasing mucosal blood flow, and stimulating afferent neurons (Matsumoto, Takeuchi, & Okabe, 1991; Takeuchi, Niida, Matsumoto, Ueshima, & Okabe, 1991). Capsaicin also enhanced the gastric defense mechanism by the release of sensory neuropeptides in the stomach. Capsaicin can bind and accelerate the TRPV1 receptor by prompting the influx of sodium and calcium and accelerating the release of inflammatory neuropeptides. It was reported that dietary capsaicin at both low (0.01%) or high (0.02%) doses can regulate obesity and glucose homeostasis by increasing the fecal butyrate and plasma total GLP-1 levels whereas reducing the plasma total ghrelin, TNF-$\alpha$, IL-1$\beta$, and IL-6 levels. It was observed to inhibit the increase of fasting blood glucose and insulin levels that seemed to be an alteration of gut microbiota in male obese diabetic ob/ob mice. The study claimed that dietary capsaicin can improve glucose homeostasis, but could not inhibit obesity-related phenotypes in obese diabetic mice (Richards, Lapoint, & Burillo-Putze, 2018; Song et al., 2017). A higher oral dose of capsaicin (50 mg/kg body weight) decreased the microsomal parameters like cytochrome P450 content and enzyme activities of aniline hydroxylase, aminopyrine demethylase, and UDP-glucuronyl transferase in rats which relay the detoxification activity of xenophobic compounds (Iwama, Tojima, Iitoi, Takahashi, & Kanke, 1990). Kang, Teng, and Chen (1996) reported that capsaicin at a dose of 5 mg/kg daily significantly showed a healing response in acetic acid-induced gastric ulceration in the rat.

Capsaicin can also be a useful treatment modality for those with hypochlorhydria and hyperchlorhydria. Several reports demonstrated that capsaicin has both inhibitory and secretory properties of stomach acid. Capsaicin at 1 mg/kg showed the highest gastric acid secretory property in rats and the dose increased to 2 mg/kg caused reduced stomach acid output (Limlomwongse, Chaitauchawong, & Tongyai, 1979). It has been also reported that an intragastrical capsaicin dose of up to 800 μg/kg inhibited the gastric acid secretion in pylorus-ligated rats in dose dependent manner with an $ID_{50}$ value of 400 μg/kg (Mózsik, Vincze, & Szolcsányi, 2001). Studies on 10 human voluntaries revealed that capsaicin dose-dependently inhibited basal $H^+$ output in the gastrointestinal tract with an $ID_{50}$ value of 400 μg (Mózsik et al., 1999). Capsaicin was also reported to induce the secretion of gastric $HCO_3^-$ (Takeuchi, Ise, Takahashi, Aihara, & Hayashi, 2015). Capsaicin stimulated gastric alkaline secretion in rats at a pH range of 4.5. The mucosal application of capsaicin at a concentration range of 0.3–6 mg/ml for 30 min significantly increased the pH and $HCO_3^-$ output in a dose-dependent manner and increased transmucosal potential difference in the duodenum and decreased in the stomach (Satyanarayana, 2006). Capsaicin increased the secretion of $HCO_3^-$ in the duodenum of in vivo rat model via the stimulation of capsaicin-sensitive afferent neurons in the presence of prostacyclin ($PGI_2$) IP receptors under influence of luminal acid (Takeuchi & Aihara, 2014; Takeuchi et al., 2015). The extract of *Capsicum* also significantly reduced oral drug availability. Orally administrated (300 mg/kg/day) of *Capsicum* extract containing 100 mg/g capsaicin for 4 weeks reduced the salicylic acid bioavailability in blood by 63% and 76%, respectively, whereas the bioavailability of aspirin in blood was undetectable. This effect led to the development of gastrointestinal impacts of both *Capsicum* extract and capsaicin (L. Cruz, Castañeda-Hernández, & Navarrete, 1999).

## 5.13 | Hypothermic activity

Dihydrocapsaicin and capsaicin from the chili showed hypothermic activity in the mouse. The subcutaneous administration of dihydrocapsaicin on cerebral and blood–brain barrier damage in cerebral ischemia and reperfusion models activated nuclear-related factor-2 (Nrf2), and decreased oxidative stress and inflammation. The effect of dihydrocapsaicin was more potential than capsaicin. Oral administration of capsaicin helped in decreasing the body temperature with a simultaneous increase in tail surface temperature of wild-type mice and it induced neuronal Fos expression in TRPV1 knockout mice. Whereas after oral administration of capsaicin, the long-lasting locomotory activity was increased in both wild-type and knockout mice and also caused TRPV1-dependent acute hypothermia (Inagaki, Kurganov, Park, Furube, & Miyata, 2019; Janyou et al., 2017). But the peripheral administration of capsaicin at a dose of 5 mg/kg produced a long-lasting fall in body temperature (Rabe, Buck, Moreno, Burks, & Dafny, 1980). Whereas, Szikszay and Obal (1982) demonstrated that single subcutaneous administration of capsaicin (10 mg/kg) produced a hypothermic effect that reached to maximum (34°C) after about

2 hr; however the higher doses (20–50 mg/kg) did not show significant fall in body temperature.

## 5.14 | Antiinflammatory activity

Several reports have demonstrated the antiinflammatory activity of capsaicin in different experimental conditions. C.-S. Kim and coworkers (2003) reported that capsaicin dose-dependently inhibited LPS-induced PGE2 production, and inhibited the enzymatic activity of COX-2 and expression of the iNOS protein in LPS-stimulated murine peritoneal macrophages. It also dose-dependently inhibited the production of pro-inflammatory cytokine TNF-α (J.-Y. Park et al., 2004). A small dose of capsaicin inhibited the production of pro-inflammatory cytokine IL-8 in *H. pylori*-infected gastric epithelial cell lines AGS and MKN45. A dose of 100 μM/L of capsaicin inhibited the production of IL-8 by 43.2 and 70% in *H. pylori*-infected MKN45 and AGS cells, respectively (I. O. Lee et al., 2007). A recent in vitro antiinflammatory activity study observed that the fruits extract of *C. annuum* showed very strong inhibition of albumin denaturation and antiproteinase activity. The in vitro study conducted by L. Chen and Kang (2013) reported the presence of a very high level of phenolic acids as chlorogenic acid (3.82 mg/g dry weight) and *p*-coumaric acid (2.98 mg/g dry weight) which are recognized as the most powerful antioxidant and antiinflammatory agent in present use. The higher content of capsaicin (10.93 mg/g) in the stalk of red peppers resulted in significant inhibition of NO production in LPS-stimulated RAW 264.7 macrophages and nitrite accumulation in a concentration-dependent manner. It was observed that the stalk extract at a concentration of 20 μg/ml displayed strong NO inhibitory activities (L. Chen & Kang, 2013; Z. Iqbal et al., 2020). Bhattacharya, Chattopadhyay, Mazumdar, Chakravarty, and Pal (2010) have carried out the activity using phenolic and flavonoid compounds present in chili and reported to have antiinflammatory activity. Luo, Peng, and Li (2011) studied the activity of capsaicinoids and capsinoids compounds from *C. annuum* and reported them to exhibit antiinflammatory activities. Mueller, Hobiger, and Jungbauer (2010) studied the antiinflammatory activity using an LPS-stimulated macrophage model and showed that chili possessed significant antiinflammatory activity.

## 5.15 | Pain modulating activity

Several capsaicinoids isolated from the chili peppers are effective molecules in several sensory nerve fibers (Sharma et al., 2013). Capsaicinoids have been studied for sensory nerve fibre disorders associated with painful arthritis, cystitis, human immunodeficiency virus, and diabetic neuropathy (Sharma et al., 2013; Smith et al., 2017). Studies have reported the nociceptor function and sensitization of capsaicin toward the affected skin of individuals with neuropathic pain observed by the cutaneous application of capsaicin. Additionally, a randomized placebo-controlled trial using 0.1% topical capsaicin showed an effective response when tested with topical clonidine (alpha-agonist hypotensive agent) during screening in painful diabetic peripheral neuropathy (Sharma et al., 2013; Smith et al., 2017). The topical capsaicin has been useful for the treatment of postherpetic neuralgia (Yong et al., 2017), diabetic neuropathy (Derry & Moore, 2012; Tandan, Lewis, Krusinski, Badger, & Fries, 1992), arthritis (Laslett & Jones, 2014), psoriasis, pruritus, cluster headache, postmastectomy pain syndrome, oral mucositis, cutaneous allergy, hematuria syndrome, neck pain, amputation stump pain, skin tumor, detrusor hyperreflexia, reflex sympathetic dystrophy, and rhinopathy (Hautkappe et al., 1998). A double-blind randomized study on 70 osteoarthritis patients and 31 rheumatoid arthritis patients showed that the topical application of capsaicin cream (0.025%) for 4 weeks remarkably reduced the pain by 57 and 33% in osteoarthritis and rheumatoid arthritis patients, respectively (Deal et al., 1991). The substance P is responsible for the pain sensation and the initial application of topical capsaicin released substance P from sensory nerve fibers but the repeated application of capsaicin cream depleted the substance P availability (Anand & Bley, 2011; Rumsfield & West, 1991). Capsaicin depleted the substance P from various sites of the body like dorsal root ganglia, dorsal spinal cord, sites of the cell bodies, and central terminals of primary afferent neurons (Burks, Buck, & Miller, 1985). Not only capsaicin, but dihydrocapsaicin could also deplete substance P from various sites (Ramírez-Romero, Gallup, Sonea, & Ackermann, 2000).

Capsaicin is used in ointments to relieve the pain of peripheral neuropathy. Derry, Rice, Cole, Tan, and Moore (2017) have shown that capsaicin acts as an analgesic to treat post-surgical and osteoarthritis pain (Derry et al., 2017). Glinski, Glinska-Ferenz, and Pierozynska-Dubowska (1991) showed that capsaicin creams are used to treat psoriasis and further reduce itching and inflammation (Glinski et al., 1991). Capsaicin was also shown to decrease rheumatoid arthritis pain, inflammatory heat, and noxious chemical hyperalgesia (Fraenkel, Bogardus, Concato, & Wittink, 2004). Anand and Bley (2011) showed that the effect of capsaicin at 8% patches (a high dose) for 12 weeks decreased the neuropathic pain in patients. Knotkova, Pappagallo, and Szallasi (2008) explained the current molecular mechanism of pain relief by capsaicin via targeting the TRPV1 receptor.

## 5.16 | Antiischemic activity

The capsaicin showed antiischemic activity in perfused rat and guinea-pig hearts. Capsaicin at a concentration of 30 μM reduced the ischemic ventricular tachycardia (by 100–0%), ischemic ventricular fibrillation (by 60–0%), and reperfusion ventricular fibrillation (by 90–33%) in the perfused rat. Capsaicin also reduced the left ventricular developed pressure by 35% in non-ischemic rat hearts and increased coronary flow by 40%. In guinea-pig hearts capsaicin dose (30 μM) reduced the reperfusion ventricular fibrillation from 100 to 10% (D'Alonzo et al., 1995).

## 5.17 | Antiarrhythmic activity

The antiarrhythmic activity of capsaicin was evaluated in the heart of the guinea-pig. The electrophysiologic evaluation in guinea-pig papillary muscles demonstrated that capsaicin doses of 10, 30, and

100 μM reduced the action potential duration from 90 to 9%, 28%, and 39% at 1 Hz respectively (D'Alonzo et al., 1995). Morgado-Valle and Feldman (2004) reported that the small dosage of capsaicin can block respiratory rhythm via the depletion of substance P and induction of glutamate release in a dose and time-dependent manner in neonatal rats. Capsaicin at the dosage of 10, 30, and 50 μM blocked the respiratory rhythm after 100–150 min, 90–110 min, and 55–60 min, respectively (Morgado-Valle & Feldman, 2004).

## 5.18 | Antiviral activity

Although there are lesser reports on the antiviral efficacy of capsaicinoids yet. Bourne, Bernstein, and Stanberry (1999) carried out the antiviral activity of is *cis*-capsaicin (Civamide) and showed that it acts actively against herpes simplex virus (HSV) ailment in guinea-pigs by blocking the viral replication cycle. While Khan et al. (2014) reported on the vanilloid capsaicin from *C. annuum* and found it to be active against the pathogenesis of HSV in animal models.

## 5.19 | Anxiolytic, muscle relaxant, and sedative activity

Jawad et al. (2017) studied the anxiolytic, muscle relaxant, and sedative activity using the crude extract and *n*-hexane fraction of *C. annuum* fruit in healthy male albino mice. The results on anxiolytic showed that 50, 100, and 200 mg/kg produced a significant ($p < .05$) reduction in the time spent in the closed arm. However, the *n*-hexane fraction was comparatively potent and evoked a highly significant ($p < .001$) effect in the 2.5, 5, and 10 mg/kg treated mice by increasing the number of entries to open arms and also time spent in the open arms. Time spent in the closed arms was also markedly decreased. The sedative activity was studied by analyzing the effects in thiopental-induced sleep-in mice and the results showed that the group treated with the crude extract at 200 mg/kg showed a significant ($p < .01$) decrease in the onset time and significantly ($p < .05$) increased the duration of sleep. The group tested with *n*-hexane fraction at a dose of 10 mg/kg elicited a significant ($p < .001$) decrease in the onset of action and significantly increased the duration of sleep (Jawad et al., 2017).

## 5.20 | Antidiabetic activity

Tsui, Razavi, Chan, Yantha, and Dosch (2007) have studied the antidiabetic effects of substance P, a neuropeptide released by capsaicin, which showed to reverse diabetic activity in mice. In humans, the substance P seems to reduce insulin release and cause changes in blood sugar levels (Brown & Vale, 1976). Razavi et al. (2006) studied the effects of capsaicin on Type-1 diabetes in neonatal diabetes-prone NOD mice and the results showed to significantly prevent the development of Type-1 diabetes via removal of these neurons, which are thought to attract pathogenic T-cells to attack pancreatic $\beta$-cells.

## 5.21 | Thermogenic and weight-reducing activity

Kawada et al. (1986) have carried out the thermogenic activity of capsaicin and the results showed that capsaicin increases the production of heat by the body for a short time. Although there is no evidence of capsaicin showing weight loss effects, there is a direct correlation between capsaicin intake and a decrease in weight regain. Lejeune et al. have carried out the effects using capsaicin in a randomized double-blind placebo-controlled study where 91 moderately overweight humans underwent a 4-week very low energy diet intervention with a weight-maintenance period and the results showed a shift in substrate oxidation from carbohydrate to fat oxidation leading to reduced appetite when compared with placebo. The study resulted in weight maintenance due to capsaicin by restraining weight regain after a weight loss of 5–10%. In this study 3-month weight-maintenance period was allowed after the completion of very-low-energy diet intervention period, where it was observed that fat oxidation after weight maintenance seemed to be elevated in the treated capsaicin group compared with placebo (Lejeune, Kovacs, & Westerterp-Plantenga, 2003). Westerterp-Plantenga et al. studied the effects of capsaicin and showed that both oral and gastrointestinal exposure resulted in increased satiety and reduces energy as well as fat intake (Westerterp-Plantenga, Smeets, & Lejeune, 2005). Diepvens, Westerterp, & Westerterp-Plantenga (2007) carried out the effects of capsaicin and reported decreasing weight to regain. Yoneshiro et al. have carried out the effects using capsaicinoids and reported increased levels of brown adipose tissue through an increase in energy expenditure. In this study, 18 healthy men aged 20–32 year underwent [$^{18}$F] fluorodeoxyglucose-positron emission tomography after 2 hr of cold exposure (19°C) while wearing light clothing. However, the ingestion capsaicin increased whole-body energy expenditure in humans which signified the antiobesity effects of capsaicin, capsinoids through activation of TRPV1 and related receptors (Yoneshiro, Aita, Kawai, Iwanaga, & Saito, 2012).

## 5.22 | Antiulcer activity

Currently, infections in the stomach with *H. pylori* disturb the normal acid secretions and thus are the reason for causing gastric ulcers (Bauer & Meyer, 2011; López-Carrillo et al., 2003). Therefore because of its irritant nature, individuals with ulcers are being advised to avoid the intake of red pepper.

Buiatti et al. (1989) have recently reported that capsaicin from red pepper does not cause ulcer formation, with numerous studies resulting that eating hot pepper plays a protective role against stomach cancer. Satyanarayana (2006) has studied the effects of capsaicin and showed it inhibits acid secretion, stimulates alkali and mucus secretions, and gastric mucosal blood flow, thus preventing the

formation of ulcers. Jancso, Kiraly, and Jancsó-Gábor (1977) have carried out the antiulcer activity and showed that capsaicin inhibited the growth of *H. pylori* and also inhibits the release of gastrin, and stimulates that of somatostatin, which decreases gastric acid secretion. J.-S. Park et al., (2000) have studied the effects of capsaicin and showed to inhibit the lipid peroxidation induced in the gastric mucosa.

## 6 | REPORTED TOXICITY OF *C. annuum* AND ACTIVE CONSTITUENTS

### 6.1 | Subchronic toxicity

The *Capsicum* extract and capsaicin were shown to influence various physiological parameters after long-term consumption. The oral administration of 50 mg/kg body weight/day capsaicin and 0.5 g/kg body weight/day *Capsicum* extract reduced the growth rate, plasma urea nitrogen, glucose, phospholipids, triglycerides, total cholesterol, free fatty acids, glutamic pyruvic transaminase, and AP in the rat (Monsereenusorn, 1983).

### 6.2 | Acute toxicity

The *C. annuum* fruit sauce was reported to produce acute toxicity in male Sprague–Dawley rats with a lethal dose ($LD_{50}$) of 23.58 ml/kg in males and 19.52 ml/kg in females in oral administration (Winek, Markie, & Shanor, 1982). Ingestion of a high amount of chili enhanced parietal secretion of pepsin, reduced potassium content, and produced gastric cell exfoliation and mucosal micro bleeding (Myers, Smith, & Graham, 1987). Oral administration of crude extract and *n*-hexane fraction of *C. annuum* fruit in healthy male albino mice showed acute toxicity with $LD_{50}$ 15 mg/kg for *n*-hexane fraction, whereas the crude extract did not show any effect (Jawad et al., 2017). While another study showed the acute toxicity of hexane fraction of *Capsicum* fruit with $LD_{50}$ 200 mg/kg and caused the death of all the mice (Johnson Jr, 2007). The acute toxicity of capsaicin was shown to be dependent on the route of administration in mice. The lethal dosages ($LD_{50}$) of capsaicin were reported to be 0.56 mg/kg (intravenous), 7.65 mg/kg (intraperitoneal), 9.00 mg/kg (subcutaneous), and 190 mg/kg (intragastric) (Kawada & Iwai, 1985). The $LD_{50}$ for the oral administration of capsaicin was 118.8 mg/kg for males and 97.4 mg/kg for female mice and 161.2 mg/kg for males and 148.1 mg/kg for female rats (Saito & Yamamoto, 1996).

### 6.3 | Cytotoxic activity

Red chili pepper consumption altered the histology of the stomach of Wistar rats. Consumption of 2 g of red pepper for 14 days produced cellular hypertrophy, congestion of blood vessels, degenerative changes distortion, and necrotic debris of the stomach (Kendabie & Adjene, 2007). Chukwu (2006) reported that the aqueous chili extract (300 mg/100 ml) produced histopathological changes like intestinal mucosal damage, necrotic columnar epithelium, and sloughed cells in the intestinal lumen, and acidification of epithelial cell cytoplasm of the albino rat. The aqueous extract also altered some morphological changes including weight loss, change in the liver color, liver cytoplasm degeneration, and loss of parenchymatous cell architecture (Chukwu, 2006).

### 6.4 | Metabolic activity

Aqueous *C. annuum* extract (2 mg/ml) did not produce any observable changes in metabolic rate but at a high concentration (15 mg/ml), the magnitude of the change in metabolic rate was very high (Chukwu, 2006). The capsaicin being structurally similar to tyrosine competitively inhibited tyrosyl-tRNA synthetase catalyzed reaction. The 97 μM ($IC_{50}$) capsaicin produced 50% inhibition of protein synthesis (Cochereau, Sanchez, & Creppy, 1997). Capsaicin at a dose of 48 μM induced 50% cell death while a higher dose (96 μM) with an equimolar concentration of tyrosine caused excessive cell death (Cochereau, Sanchez, Bourhaoui, & Creppy, 1996). Capsaicin and dihydrocapsaicin were found to inhibit the electron-transfer activity of NADH-coenzyme Q oxidoreductase in beef heart mitochondria with a lower inhibitory property of capsaicin than dihydrocapsaicin (Shimomura, Kawada, & Suzuki, 1989).

### 6.5 | Carcinogenic or mutagenic activity

Chili extract has been reported to induce carcinogenesis in the stomach and liver in BALB/c mice (Agrawal, Wiessler, Hecker, & Bhide, 1986). The red chili also reacted as a co-carcinogen when administered with 100 μg/ml *N*-methyl-*N*′-nitro-*N*-nitrosoguanidine. It induced the incidence of tumor formation in August Copenhagen Irish (ACI) and Fisher inbred rats by 57% in ACI rats (received 1% red pepper) and 63% in Fisher rats (received 1 or 3% red pepper; J.-P. Kim et al., 1985). Pure capsaicin also showed mutagenic or carcinogenic activity (Jang & Kim, 1988; Nagabhushan & Bhide, 1985; Toth & Gannett, 1992; Toth, Rogan, & Walker, 1984) by administration of 0.03125% capsaicin-induced tumor in 22% of female and 14% of male Swiss mice (Toth & Gannett, 1992). Hwang et al. (2010) reported the activity of capsaicin associated with skin cancer, while the incidence of gall bladder cancer was reported on consuming high amounts of red chili pepper (Asai et al., 2012; Tsuchiya et al., 2011). Yet the study by Szallasi and Blumberg (1999) showed contradictory mutagenic effects of capsaicin in the mammalian system.

### 6.6 | Genotoxic activity

The chili consumption sometimes produced exfoliation of gastric surface epithelial cells in humans with a dosage of 1.6 and 0.8 g/hr chili significantly increased the DNA content of gastric aspirate (Desai,

Venugopalan, & Antia, 1973). From the sister chromatid exchange assay and cytokinesis-block micronucleus assay, it was found that capsaicin (10–200 μM) increased micronuclei formation and exchange of sister chromatid in human lymphocytes (Marques, Oliveira, Chaveca, & Rueff, 2002). In relation to this activity, excessive chili consumption increased the risk of gastric cancer (Kwon, 2021; Zaidi, Ahmed, Saeed, Khan, & Sugiyama, 2017). Singh, Asad, Ahmad, Khan, and Hadi (2001) reported that capsaicin and dihydrocapsaicin generate ROS that break down the calf thymus and plasmid DNA in the presence of Cu(II). In the presence of Cu(II), CYP1A2 and the partial presence of CYP 2D6 induced DNA double base nick at 5′-TG-3′, 5′-GC-3′ and CG of the 5′-ACG-3′ sequence. The 5′-ACG-3′ sequence is a complementary sequence of codon 273 is responsible for the expression of p53 genes (Oikawa, Nagao, Sakano, & Kawanishi, 2006). The genotoxic effect of capsaicin was also observed in human neuroblastoma cells SHSY-5Y by the administration at 60 μM with [(3)H]L-leucine that inhibited 50% of the protein synthesis and DNA strand break leading to cell death and/or mutagenesis (Richeux, Cascante, Ennamany, Saboureau, & Creppy, 1999).

### 6.7 | Occupational asthma

The powdered fruit is sometimes associated with asthmatic reactions in humans. In the ELISA-inhibition assay it was found that 10% (w/v) dry powdered produced a cross-reaction among the IgE-binding components. Bronchial inhalation of *Capsicum* powder produced an immediate asthmatic reaction with a maximum fall in forced expiratory volume (FEV1) by 26% in a second (Sastre, Olmo, Novalvos, Ibanez, & Lahoz, 1996).

### 6.8 | Neurotoxic activity

Capsaicin showed a variety of toxic effects on sensory neurons. Administration of capsaicin degeneration of B-type primary afferent neurons located in spinal and cranial sensory ganglia in newborn mammals. Neonatal capsaicin treatment irreversibly abolished the capsaicin-sensitive primary sensory neurons by decreasing peptide content in the sensory neurons. Morphological observation revealed that neonatal capsaicin degenerates unmyelinated afferent nerve fibers, and altered the chemistry and function of sensory neurons. Capsaicin injection in subarachnoid space produced an irreversible abolition of the "afferent" function of capsaicin-sensitive primary sensory neurons (Jancso, Kiraly, Such, Joo, & Nagy, 1987). The subcutaneous administration of capsaicin (50 or 100 mg/kg) induced the corneal lesions via the destruction of the trigeminal nerve (Shimizu et al., 1984). Capsaicin has been reported to activate a receptor-operated channel, $Ca^{2+}$ ion influx, and the subsequent activation of $Ca^{2+}$-sensitive proteases which lead to the death of the subpopulation of sensory neurons (Chard, Bleakman, Savidge, & Miller, 1995). The capsaicin (50 mg/kg) also significantly reduced the number of axons/unit length of the tracheal epithelium in rats (Hoyes, Barber, & Jagessar, 1981).

### 6.9 | Inflammatory activity

Capsaicin produced a burning sensation in the skin. It was reported that capsaicin increased the expression of inflammatory cytokine IL-8 in the human epithelial BEAS-2B cell line. Because the capsaicin at a dose concentration, 10 μM increased the intracellular calcium ion concentration which stimulates the inflammatory cytokine transcript to release cytokine proteins (Veronesi, Carter, Devlin, Simon, & Oortgiesen, 1999). The capsaicin also produced neurogenic inflammation. Application of 1% capsaicin in the temporomandibular joint region of Sprague–Dawley rat dose-dependently produced edema and tissue expansion (Tang, Haas, & Hu, 2004). Winek et al. (1982) reported that fruit sauce also produced skin and eye irritation in albino rabbits.

## 7 | ROLE OF *CAPSICUM* IN CARDIAC METABOLIC HEALTH

Coronary heart disease (CHD) is the leading cause of death in all age groups. Recent epidemiological studies reviles that low-density lipoprotein cholesterol, considered bad cholesterol, usually makes the wall of the arteries harder and narrow which makes it difficult for enough oxygen-rich blood to flow through arteries to the heart (Patanè, Marte, Di Bella, Cerrito, & Coglitore, 2009). This causes an increased risk of coronary heart disease by releasing chemicals like bradykinin which is responsible for triggering major medical emergencies like a heart attack. *Capsicum* species, the nature's gift *C. annuum* L. are rich in phenolics, flavonoids, vitamins, tachykinins, and alkyl vanillylamides (Owman, 2019). The capsaicinoids, straight-chain alkyl vanillylamides are the chief chemical entity of *C. annuum* and are most effective use as a preventive treatment of CHD and heart problems (Luo et al., 2011; Patanè et al., 2009). The tachykinins, epitomized by substance P (SP), contribute to vital physiological processes like respiratory, nervous, immunological, gastrointestinal, inflammatory, and so on, and also act as vasodilators to prevent CHD. The earlier report suggested that afferent neurons containing calcitonin gene-related peptide (CGRP), SP, and neurokinin A (NKA) are very sensitive to capsaicin resulting in depolarization of peripheral nerve endings (Figure 8; De Logu, Nassini, Landini, & Geppetti, 2018; Owman, 2019). The TRPV1 which is widely distributed in nerve endings of the brain region is regulated by capsaicin. Capsaicin can trigger $NK_1R$ endocytosis in neurons as a TRPV1 agonist and thus acts as a valuable therapeutic benefit for neurodegenerative and CVD (Figure 8; De Logu et al., 2018; Luo et al., 2011; D. Zhang et al., 2021).

The investigation showed that *Capsicum* extracts can use as nutraceuticals to promote human umbilical vein endothelial cells consequently reducing cardiovascular risk (Frydas et al., 2013). Earlier reports suggest that high antioxidant-rich food materials usually show beneficial effects to reduce the risk factors of CHD. The in vitro and in vivo clinical studies reported that *Capsicum* extracts and capsaicinoids are rich in antioxidant properties and hence these secondary metabolites can provide well protection to the cells from LDL

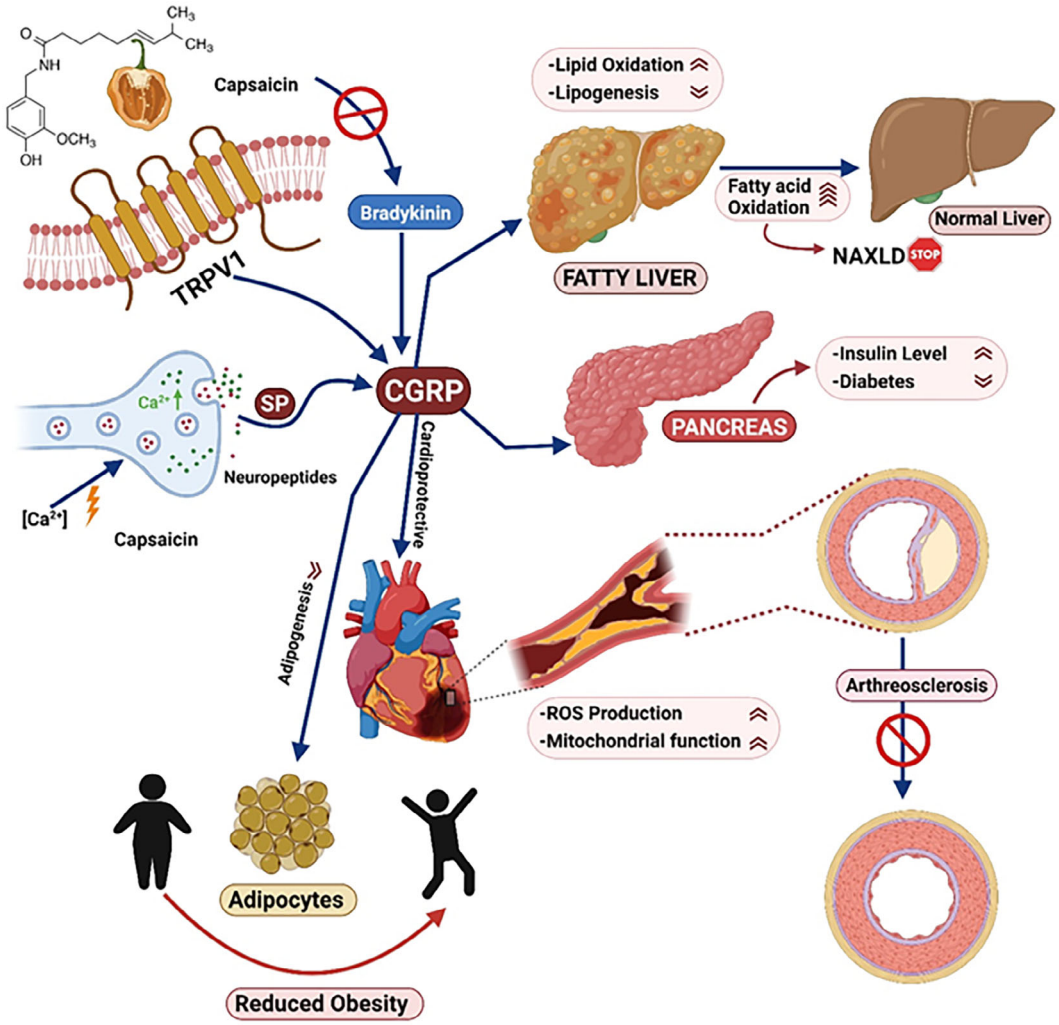


**FIGURE 8** Capsaicin modulates cardiovascular functions and protective action on CVS by producing effects on TRPV1, CGRP, SP, sensory nerve endings, ion channels for the management of obesity, hypertension, *diabetes mellitus*, atherosclerosis, and acts on cardiac endothelial cells showing cardioprotective effect. The effects of capsaicin help the inactivation of TRPV1 which has shown neuroprotective action by activating calcium-dependent enzymes, promoting the nigrostriatal dopaminergic neuronal functions allied with an abridged expression of proinflammatory cytokines and ROS/reactive nitrogen species. Capsaicin with activation of TRPV1 helps in the treatment of liver disease by downregulating lipogenesis, upregulate lipid oxidation, increasing the hepatic uncoupling protein 2 (UCP2) expressions, and thus elevating the fatty acid oxidation, stoppage of non-alcoholic fatty liver disease (NAFLD). CGRP, the most powerful vasodilator, is stimulated by Capsaicin through the activation of TRPV1 and thereby regulates or decreases the blood pressure in relief from hypertension. The cardioprotective effect is observed by the elimination of capsaicin-sensitive afferents mediated through CGRP by interacting cardiac vanilloid receptor and nitric oxide release, leading to vasodilatation. Capsaicin activated TRPV1 to enhance the PKAUCP2 pathway, downregulate ROS production, improvement of mitochondrial function to prevent atherosclerotic lesions. Activation of Capsaicin inhibits the severity of obesity by activating TRPV1 which reduces the weight of adipose tissues, and decreases lipid storage by elevating lipid oxidation. Capsaicin upon the action of TRPV1 eliminates CGRP, SP which can reduce the complications of hypertension, obesity, atherosclerosis, and fatty liver following various pathways, all together directly/indirectly to protect against cardiovascular diseases

oxidation, protein nitration, and also from apoptosis (Qin et al., 2017). The literature suggests that a very low concentration of *Capsicum* extract (10 μg/ml) and capsaicin (1 μM) can protect from LPS-induced apoptosis. The report also suggests the antiinflammatory properties of capsaicin can reduce the inflammation when plaque developed in blood vessel walls to reduce the risk of heart attack interim developing immunity.

Capsaicin can modulate endocrine/paracrine actions and cardiovascular functions with chronic inflammatory conditions up-regulated by SP receptors (Nelson & Bost, 2004). The pharmacodynamic impacts of capsaicin on the cardiovascular system (CVS) may have a direct effect on cardiac vanilloid receptors (Szabados et al., 2020; Zahner, Li, Chen, & Pan, 2003), or through the interaction of vanilloid receptors with purinergic receptors, concurrently releasing nitric oxide (NO), leading to vasodilatation (Chularojmontri, Suwatronnakorn, & Wattanapitayakul, 2011). Interaction at $K^+$ channels or liberation of neuropeptides or vanilloid-sensitive innervation of the heart due to calcitonin-gene-related-peptide is also trait of capsaicin (Ashina et al., 2020).

The role of capsaicin is to stimulate the release of CGRP by activating TRPV1 (Figure 8). It acts as an agonist of the capsaicin receptor, and selectively binds to TRPV1 by inhibiting inflammation pathways, thus downregulation of heat shock following the upregulation of the olfactory receptor (Juturu, 2016; Zsiborás et al., 2018). Its effect on the sensory nerve system has been reported as the protective outcome of CVS with the release of multiple neurotransmitters such as CGRP, SP, and so on (Figure 8; De Logu et al., 2018; Szabados et al., 2020). The earlier report suggests that the effects of capsaicin and dihydrocapsaicin can reduce serum total cholesterol and lipid peroxide. Thus, the regular intake of the required amount of chili can be very useful to prevent CVD, atherosclerosis, and CHD as these capsaicinoids are highly antioxidant. Some studies suggested that the use of capsaicin could downregulate the *m*RNA hepatic 3-hydroxyl-3-methylglutaryl CoA reductase and cholesterol 7$\alpha$-hydroxylase and upregulated TRPV1 to enhance the PKAUCP2 pathway by reducing ROS production with the improvement of mitochondrial function to prevent atherosclerosis (Figure 8; Juturu, 2016; Patanè et al., 2009; Xiong et al., 2016). It also helps to regulate energy metabolism, trim down the weight of adipose tissues, and rising lipid oxidation, thus inhibiting the severity of the obesity problem (Figure 8), if *Capsicum* is used regularly. In conclusion of all earlier research reports, capsaicin is beneficial for the management of obesity, hypertension, *diabetes mellitus*, and atherosclerosis, and thus use of *Capsicum* help to control CVDs (Figure 8; Szabados et al., 2020).

The use of capsaicin can effectively raise the levels of serum fasting high-density lipoprotein cholesterol (HDL-C) at a dose of 3 mg/dl which resulted in a nearly 9% reduction in CVD risk. The reported clinical trials in adults with low HDL-C additionally showed effectual results of increased fasting HDL-Cat a dose of 4 mg of capsaicin for a period of 3 months (Qin et al., 2017).

## 8 | PHARMACOKINETICS OF *CAPSICUM* AND ITS RELATED COMPOUND CAPSAICIN

Toth and Gannett (1992) studied the absorption levels of capsaicin and showed at a 3 mg dose (85%) it is rapidly absorbed in the stomach within 3 hr. Philip et al. studied the absorption and metabolism of capsaicin at a dose of 5.12 mg/mice/week and the result showed a plasma concentration of male (51.5 ng/ml) and female (84.8 ng/ml) mice, respectively. Another study by Philip et al. showed that capsaicin was applied topically on the mice and the results showed that the plasma concentration after 24 hr showed that capsaicin was detected in the blood (Philip, Baroody, Proud, Naclerio, & Togias, 1994). Kawada, Suzuki, Takahashi and Iwai (1984) studied the absorption using 0.8 g of gel containing 0.075% of capsaicin and applied it to the skin of individuals and the results on average absorbed dose showed after 8 hr was 22.7 $\mu g/cm^2$.

Akagi et al. (1998) showed the absorption levels of capsaicin in the brain and spinal cord after 3 min of dosing and lesser levels were absorbed in the liver and blood after 10 min of dosing. Suresh and Srinivasan (2010) studied the tissue distribution and elimination of capsaicin at 30 mg capsaicin/kg body weight in rats and the results showed a maximum distribution of 24.4% at 1 hr which was about 94.4% absorption of capsaicin.

Toth and Gannett (1992) have shown that 10% of capsaicin was administered in rats and found to be excreted unchanged after 48 hr of administration. Richoux and Chanda et al. studied the metabolism of capsaicin and showed it to occur in the rat liver (Chanda, Sharper, Hoberman, & Bley, 2006; Richeux et al., 1999). Reilly and Yost (2006) studied the metabolism of capsaicin by CYP450 enzyme that follows several pathways and produces a variety of metabolites, which are associated with increased toxicity. A recent study by Reilly et al. (2013) studied the metabolism of capsaicin by the CYP450 enzyme and showed conflicting reports related to the cytotoxic, pro-carcinogenic, and chemoprotective effects. Therefore, a wide number of reports stated that capsaicin had shown to possess better absorption and metabolism.

Chaiyata, Puttadechakum, and Komindr (2003) studied the metabolic rate (MR) using 5 g of fresh chili pepper administered in Thai women and the results showed to increase in the MR and lasted up to 30 min. Chaiyasit, Khovidhunkit, and Wittayalertpanya (2009) studied that administering *capsicum* (5 g gel capsules) in humans showed to maintain insulin levels. Saria, Skofitsch, and Lembeck (1982) studied the effect of capsaicin and showed liver metabolism. The analysis of the metabolic effects of capsaicin in CYP450 in vitro via liver microsomes showed that the metabolism was faster and quicker in the rat and human hepatic microsomes (Reilly et al., 2003). Mózsik, Past, Salam, Kuzma, and Perjési (2009) studied the effects of capsaicin administered and the results showed that about 6.3% was expelled in feces. Thus, approximately about 94% of capsaicin were digested and utilized, whereas only small amounts of 0.095% were excreted in urine (Mózsik et al., 2009). Kawada et al. (1984) have carried out the absorption of capsaicin in vivo study in rats and the results showed that about 85% of capsaicin were absorbed within 3 hr. A study on the metabolites of capsaicin namely 16-hydroxycapsaicin, 17-hydroxycapsaicin, and 16- and 17-dihydrocapsaicin showed that only small amounts were excreted in the feces and urine (Cortright & Szallasi, 2004).

## 9 | FOOD SAFETY OF CONSUMPTION OF *CAPSICUM* AND CAPSAICIN

*Capsicum* and its capsaicinoids are consumed worldwide and have a long history of controversy regarding its safety in consumption or topical application. A wide number of epidemiologic studies showed that capsaicin acts as a cancer preventive agent or carcinogen. Even though there are not many extensive studies have been carried out on the safety aspects of red pepper, few reports showed on consuming red pepper in the Indian population that it has no adverse effects on growth, organ weights, feed efficiency ratio, nitrogen balance, and blood chemistry (Sambaiah, Ratankumar, Kamanna, Satyanarayana, & Rao, 1982). Narasimhamurthy (1988) has shown that consuming capsaicin did not induce any mutagenic effects in mice. Further,

capsaicin-containing creams are reported to relieve pain. Bode and Dong (2011) studied the effect of long-term topical application of capsaicin and showed it to be beneficial against skin carcinogenesis in mice. Therefore based on these reports red pepper and capsaicin are highly safe to be consumed.

### 9.1 | Doses

For external uses, *Capsicum* creams and capsaicin are accessible in a wide number of ways, from capsaicin ranging from 0.025 to 0.075%, are applied 3–5 times/day. K. S. Kim, Kim, Hwang, and Park (2009) studied that *Capsicum* plasters containing 345.8 mg of powdered *Capsicum* and 34.58 mg of *Capsicum* tincture and showed to be beneficial against postoperative pain and nausea. Simpson and Steinberg et al. used a higher concentration of 8% capsaicin dermal patch and showed it to be beneficial in HIV-linked neuropathy (Simpson, Brown, & Tobias, 2008) and intractable pain (Steinberg, Oyama, Rejba, Kellogg-Spadt, & Whitmore, 2005). Lysy et al. (2003) studied using a low concentration of capsaicin (0.006%) ointment and showed it to be utilized in the itching in pruritus ani, and with a higher concentration causing anal burning.

## 10 | CONCLUSION AND FUTURE DIRECTION

*Capsicum annuum* is a well-known spice generally used as a flavoring agent worldwide and important traditional medicine. Its fruits have been traditionally used to treat various diseases by virtues of herbal catalyst, stimulant, and circulation enhancer, as well as a potential activator of the mucus membrane. A comprehensive analysis of recently published research articles showed that it has a great role in gastroprotection and as an antimutagenic or anticarcinogenic agent. Other important pharmacological activities include antimicrobial, antioxidant, immunomodulatory, cardiovascular, antihyperlipidemic, anti-inflammatory, pain modulating, antiischemic, and so on. The chemical investigation of *C. annuum* extracts revealed that capsaicin, dihydrocapsaicin, and carotenoids are the predominant principal constituents, which are attributed to various pharmacological activities. Especially, the capsaicinoids' activities such as anticancer activities through apoptosis activation and cardiovascular activities through the restoration of CGRP activity have been widely studied.

Future studies are also necessary to evaluate the possible synergistic activity of *Capsicum* extracts or active compounds such as capsaicin with other therapeutic agents used for the treatment of various diseases. Similarly, possible herb–drug interactions should also be studied in detail. At a low concentration, capsaicin showed various pharmacological activities but at a higher dose concentration, it showed toxic effects on both in vivo and in vitro models. These data need satisfactory improvement to prove the therapeutic efficacy of *C. annuum* fruit in cardiovascular diseases, gastroprotection, and other uses. Thus, further pre-clinical and clinical studies would be necessary to explore the potential health-beneficial effects of *C. annuum* and capsaicin.

### CONFLICT OF INTEREST

The authors declare no conflicts of interest.

### DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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