Pharmacological Research - Modern Chinese Medicine 6 (2023) 100222

Contents lists available at ScienceDirect

Pharmacological Research - Modern Chinese Medicine

journal homepage: www.elsevier.com/locate/prmcm

Review

Curcuma longa (Turmeric): Ethnomedicinal uses, phytochemistry, pharmacological activities and toxicity profiles—A review

Emeka J. Iweala[a], Miracle E. Uche[b], Emmanuel Dike Dike[b], Lotanna Richard Etumnu[b], Titilope M. Dokunmu[a], Adurosakin E. Oluwapelumi[c], Benedict Chukwuebuka Okoro[a,b], Omoremime E. Dania[a], Abiodun H. Adebayo[a], Eziuche Amadike Ugbogu[b,*]

[a] Department of Biochemistry, Covenant University, PMB 1023 Ota, Ogun State, Nigeria
[b] Department of Biochemistry, Abia State University, PMB 2000 Uturu, Abia State, Nigeria
[c] Ladoke Akintola University of Technology, PMB 4000 Ogbomoso, Oyo State, Nigeria

ARTICLE INFO

Keywords:
Curcuma longa
Turmeric
Phytochemistry
Pharmacological activities
Ethnomedicinal properties
Bioactive compounds

ABSTRACT

Introduction: *Curcuma longa*, popularly known as Turmeric, is a rhizomatous herbaceous perennial plant used in folk medicine for the treatment, prevention, and management of various illnesses such as cancer, diabetes, Arthritis, diarrhoea, inflammation, psoriasis, hepatobiliary diseases, gastric and peptic ulcers.

Results: This study reviewed the ethnomedicinal potentials, phytochemicals, and pharmacological activities of *C. longa*. *In vitro* and *in vivo* studies reported that *C. longa* and its major bioactive constituent (curcumin) possess various pharmacological properties. These include; anticancer, antidiabetic, anti-osteoarthritis, antidiarrheal, cardioprotective, anti-oxidative, neuroprotective, hepatoprotective, anti-microbial, renoprotective and anti-inflammatory activities. This review demonstrated that the various pharmacological activities of *C. longa* might be attributed to the presence of numerous bioactive compounds. However, these varying potentials have not been effectively analysed for optimal application in developing new therapies. Also, the applicability and mode of action of the different bioactive compounds found in *C. longa* have not been fully exploited.

Conclusion: This study showed that *C. longa* could be exploited by pharmaceutical industries to develop pharmaceutical products. However, there is a need for human clinical trials and quality control studies to establish effective and safe doses of *C. longa* and its major bioactive constituent-curcumin suitable for treating several diseases.

1. Introduction

Globally, medicinal plants and their bioactive constituents have found practical applications in treating, managing, and preventing various human and animal diseases in complementary and orthodox medicines. Recently, it has been reported that about 80% of the world's population depends on medicinal plants and their phytoconstituents (bioactive compounds) for their primary health care [1–3]. Interestingly, the preference for the use of medicinal plants over orthodox medicines may be due to the efficacies of their bioactive agents as well as other factors such as accessibility, affordability, availability and their acclaimed less toxic effects [3–5]. Due to these current possibilities, medic-

List of abbreviations: ABTS, 2, 2′-Azino-Bis-3-Ethylbenzothiazoline-6-Sulfonic Acid; AcylCpCpx, Diacetylcurcumin manganese complex; AFB1, Aflatoxin B1; ALP, Alkaline phosphatase; ALT, Alanine amino transferase; AST, Aspartate aminotransferase; β-FGF, Basic fibroblast growth factor; CAT, Catalase; CCl_4, Carbon tetrachloride; CFA, Freund's Complete Adjuvant; COX-2, Cyclooxygenase-2; CpCpx, Curcumin manganese complex; DPPH, 2,2-diphenyl-1-picrylhydrazyl; DVB/CAR/PDMS, Divinylbenzene/Carboxen/Polydimethylsiloxane; EGFR, Epidermal growth factor receptor; EH, Epoxide hydrolase; EtOAc, Ethyl acetate; FRAP, Ferric reducing antioxidant power assay; GC–MS, Gas Chromatography/Mass Spectrometry; GC-SAW, Gas chromatography combined with surface acoustic wave sensor; GGT, Gamma-glutamyl transferase; GPx, Glutathione peroxidase; GST, Glutathione S-transferase; HO-1, haem oxygenase; HPLC, High-performance liquid chromatography; HR-ESI-MS, High-resolution electrospray ionization mass spectrometry; LDH, Lactate dehydrogenase; MAE, Microwave-Assisted extracted; MAHD, Microwave-assisted hydrodistillation; MDA, Malondialdehyde; MeOH, Methanol; MMP-2, Matrix metalloproteinase-2; MMP3, Matrix metalloproteinase; NMBA, N-nitrosomethylbenzylamine; NMR, Nuclear Magnetic Resonance; OVA, Ovalbumin; PARP, Poly (ADP-ribose) polymerase; PLE, Pressurized liquid extraction; RBC, Red blood cells; ROS, Reactive oxygen species; RT-PCR, Reverse transcription polymerase chain reaction; SALP, Serum alkaline phosphatase; SOD, Superoxide dismutase,; STZ, Streptozotocin; TAA, Thioacetamide; TGF-β, Transforming growth factor; TNBS, 2,4,6-Trinitrobenzene sulphonic acid; UV, Ultraviolet; VEGF, Vascular endothelial growth factor; WBC, White blood cells.

* Corresponding author.
E-mail address: amadike.ugbogu@abiastateuniversity.edu.ng (E.A. Ugbogu).

https://doi.org/10.1016/j.prmcm.2023.100222
Received 13 December 2022; Received in revised form 9 January 2023; Accepted 17 January 2023
Available online 22 January 2023

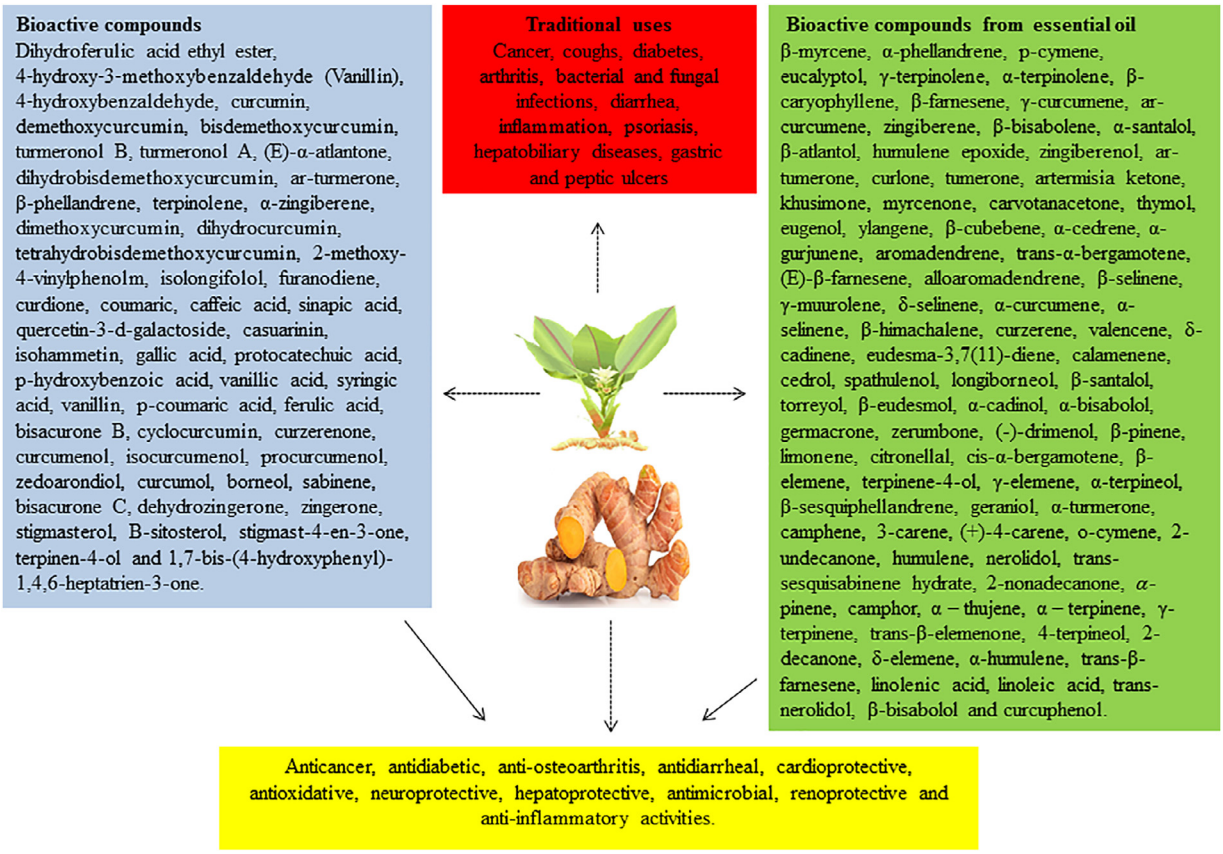

Fig. 1. Traditional uses, bioactive constituents, and pharmacological activities of *C. longa*.

inal plants and their bioactive constituents have attracted the attention of numerous scientists from various disciplines leading to their exploration as natural therapeutic agents in developing new drugs and pharmacological products [6,7]. Also, medicinal plants have been explored in traditional medicine to treat chronic and life-threatening diseases such as diabetes, hypertension, and cancer [3,8,9]. Amongst the well-known plants that have been utilized, *Curcuma longa* is one whose therapeutic efficacy has been identified in treating several human diseases.

Curcuma longa, commonly known as Turmeric, is a rhizomatous herbaceous perennial plant belonging to the Zingiberaceae family [10]. It originated in India and is widely cultivated in China, Sri Lanka, West and East Africa and other tropical countries. It is known as Jianghuang or Huangjiang in China. It is used in Chinese Traditional Medicine (TCM) for the treatment, prevention and management of various illnesses such as cancer, coughs, diabetes, Arthritis, diarrhoea, inflammation, psoriasis, hepatobiliary diseases, skin disorders, gastric ulcers and peptic ulcers [10,11]. It promotes blood circulation, removes stagnation, alleviates depression, and serves as a natural flavouring agent that strongly affects food's colour, taste and nature [12].

Furthermore, several studies have shown that *C. longa* and its bioactive compounds possess numerous pharmacological activities such as antioxidant [13], hepatoprotective [14], anti- osteoarthritis [15], anti-inflammatory [16], anticancer [17], anti-arthritic [18], neuroprotective [19], antidiabetic [20], antidiarrheal activity [21], anti-microbial [22], anti-atherosclerotic, antidepressant, anti-ageing, wound healing and memory enhancing activities [10,23]. The use of Turmeric in traditional medicine is supported by the presence of more than 300 biologically active components such as polyphenols, sesquiterpenes, diterpenes, triterpenoids, sterols, and alkaloids (Fig. 1). The typical yellow colour of Turmeric is due to curcuminoids, a class of phenolic compounds present in turmeric [24]. Curcuminoids make up 2–9% of Turmeric, depending on its origin and soil fertility levels in the region where it was cultivated [25]. The four main curcuminoids are curcumin (77%), desmethoxycurcumin (17%), bis-desmethoxycurcumin (3%) and cyclocurcumin (a minor constituent) [25,26]. Curcumin (an active phytochemical in Turmeric) has shown promise in effectively reducing lipid levels in patients with type-2 diabetes mellitus and metabolic syndrome. Also, it is said to be cardioprotective because it can reduce C-reactive protein levels [27]. In China, elemene, a compound obtained from Turmeric, has been approved for cancer treatment [23].

Therefore, this present review comprehensively evaluated scientific studies and provided up-to-date information on the ethnomedicinal uses, bioactive constituents and pharmacological activities of *C. longa*. This study also identifies scientific gaps in current knowledge and the need for in-depth study on the mechanisms, efficacy, safe doses and commercialization of *C. longa* for treating various human and animal diseases.

2. Materials and methods

The materials used in this study were obtained from the following databases; Science direct (https://www.sciencedirect.com/), Springer (https://www.springer.com/gp), Wiley (https://www.wiley.com/en-us), MDPI (https://www.mdpi.com/), Frontiers (https://www.frontiersin.org/) and PubMed (https://pubmed.ncbi.nlm.nih.gov/). The key search terms or words were Curcuma longa or Turmeric alone or in combination with any of the following keywords; botanical description, ethnopharmacological uses, geographical distribution, taxonomy, phytochemicals, biologically active constituents, essential oils and pharmacological activities. Only peer-reviewed papers published in the English language were used in this study. The biologically active constituents identified from C. longa and its essential oils were searched in the Webbook, NIST Chemistry, PubChem and ChemSpider databases and drawn with ChemDraw (version 12.0.2).

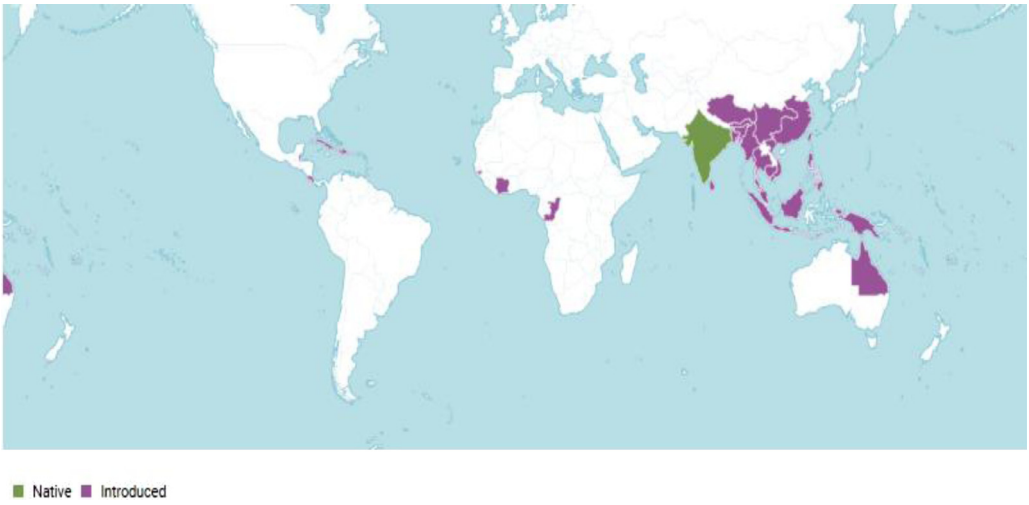

Fig. 2. Map of worldwide distribution of *Curcuma longa* L., the green colour shows the native regions, and the pink colour represents the introduced countries.

3. Botanical description, geographical distribution

3.1. Botanical description

Curcuma longa is a member of the Zingiberaceae family. It is a perennial herbaceous plant that grows up to 2 m without stem and rhizomes-stock but with erect leafy shoots bearing up to twelve (12) leaves. The leaves grow up to 1 m and are oblong or lanceolate, dark green from the upper path and pale green from beneath. The sheath and petiole have a similar length to the blade. *Curcuma longa* has a sterile, pale yellow and reddish flower, whereas its flowering bract is green with a purplish colour [28,29]. *Curcuma longa* has a rhizome that grows below the soil [30]. The plant is mainly cultivated for its rhizome, characterized by rough segmented skins [30]. The rhizome can grow to a length of 2.5–7.0 cm with a diameter of 2.5 cm [30]. The rhizome has a balmy smell and bitter taste. *Curcuma longa* plants are grown in tropics and subtropic regions at around 20 ˚C and 30 ˚C with sufficient rainfall [31].

3.2. Geographical distribution

Curcuma longa (Turmeric) is indigenous to Indian and widely distributed in the following countries: Andaman Is., Assam, Borneo, Bangladesh, Belize, China South-Central, China Southeast, Cambodia, Caroline Is., Cook Is., Costa Rica, Cuba, Comoros, Congo, Nigeria, Dominican Republic, East Himalaya, Easter Is., Fiji, Gilbert Is., Guinea-Bissau, Gulf of Guinea Is., Haiti, Hawaii, Ivory Coast, Jawa, Leeward Is., Lesser Sunda Is., Malaya, Marquesas, Mauritius, Myanmar, New Caledonia, New Guinea, Nicobar Is., Philippines, Pitcairn Is., Puerto Rico, Queensland, Réunion, Samoa, Society Is., Sri Lanka, Sumatera, Solomon Is., Taiwan, Thailand, Tibet, Tonga, Trinidad-Tobago, Tuamotu, Tubuai Is., Vietnam and Windward Is (https://powo.science.kew.org/taxon/urn:lsid:ipni.org:names:796451–1}distribution-map) Fig. 2.

4. Traditional/ethnomedicinal uses

Curcuma species are used in Asian countries like Bangladesh, Malaysia, India, Nepal, and Thailand for treating pneumonia, bronchial complaints, leucorrhoea, diarrhoea, dysentery, infectious wounds or abscesses and insect bites [32]. Primordial and current medicinal practices in India utilize Turmeric to treat jaundice, rheumatism, cough and several disorders [33]. Emphasizing curcumin's maximal ethnomedicinal efficiency in India, Vaughn [27] reported its use in treating obesity and inflammation. In Pakistan, powdered *C. longa* extract is used in curing pimples and wounds [34]. An ethnomedicinal survey in Nepal by Singh et al. [35] reported that paste derived from the rhizome of *C. longa* could be applied to treat wounds and injuries. The juice from its leave has an anthelmintic effect and serves as a blood purifier [35]. The juice obtained from powdered *C. longa* is also utilized in the Philippines for the treatment of Arthritis [36]. In the Kurdish community of Iraq, leaves from *C. longa* are used in facial massages and the treatment of Arthritis. At the same time, the decoction obtained from the rhizome has been reported for its anticancer activity [37]. In Korea, Kim and Song [38] have also stated its usage in treating gastroenteric disorders. Merzouki et al. [39] reported that the oral intake of *C. longa* powder aids digestion and could serve as a calefacient and also reported using extracts from the rhizome as a condiment for cooking in Morocco. An extensive ethnoveterinary survey in Trinidad and Tobago, as reported by Lans et al. [40], revealed the diverse therapeutic efficacy of different parts of *C. longa* on horses. The survey reported how the rhizomes from *C. longa* were pounded and used in treating horses' hoofs and how the powder from the plant's rhizome was used to treat Arthritis. In Colombia, the plant is used to treat diabetes, obesity, prevent indigestion, and thrombosis, amongst several therapeutic activities [41]. Curcumin derived from the rhizomes of *C. longa* has been identified as an ancient remedy to a broad spectrum of diseases and is also utilized by diverse communities, most notably the Asian community, with applications dating back over 2500 years [42].

5. Phytochemistry

5.1. Phenolic compounds

Phytochemical analysis of different parts of *C. longa* revealed many bioactive phenolic compounds across a wide range of studies wherein different identification methods were utilized (Fig. 3). Czernicka et al. [43] identified phenolic compounds such as dimethoxycurcumin, dihydrocurcumin, and tetrahydrobisdemethoxycurcumin using a mass spectrometer coupled with liquid chromatography (LC-ESI-Q-TOF-MS) to analyse methanol and diethyl ether extracts of C. longa rhizome. Cyclocurcumin was identified through spectroscopic analyses (H NMR, C NMR, HSQC, HMBC, and NOESY) of ethanol extract of *C. longa* rhizomes [44].

Also, through the GC-MS and HPLC analysis of methanol extract of *C. longa* rhizomes, as well as IR, H, and C NMR analysis [45], compounds such as 2-methoxy-4-vinylphenol and isolongifolol were identified. Sabir et al. [46] characterized phenolic compounds, including coumaric, caffeic acid, sinapic acid, quercetin-3-D-galactoside, casuarinin, and isohammetin through the HPLC analysis of ethanol extract of *C. longa* rhizome. Alternatively, gallic acid, protocatechuic acid, p-hydroxybenzoic acid, vanillic acid, syringic acid, vanillin, p-coumaric

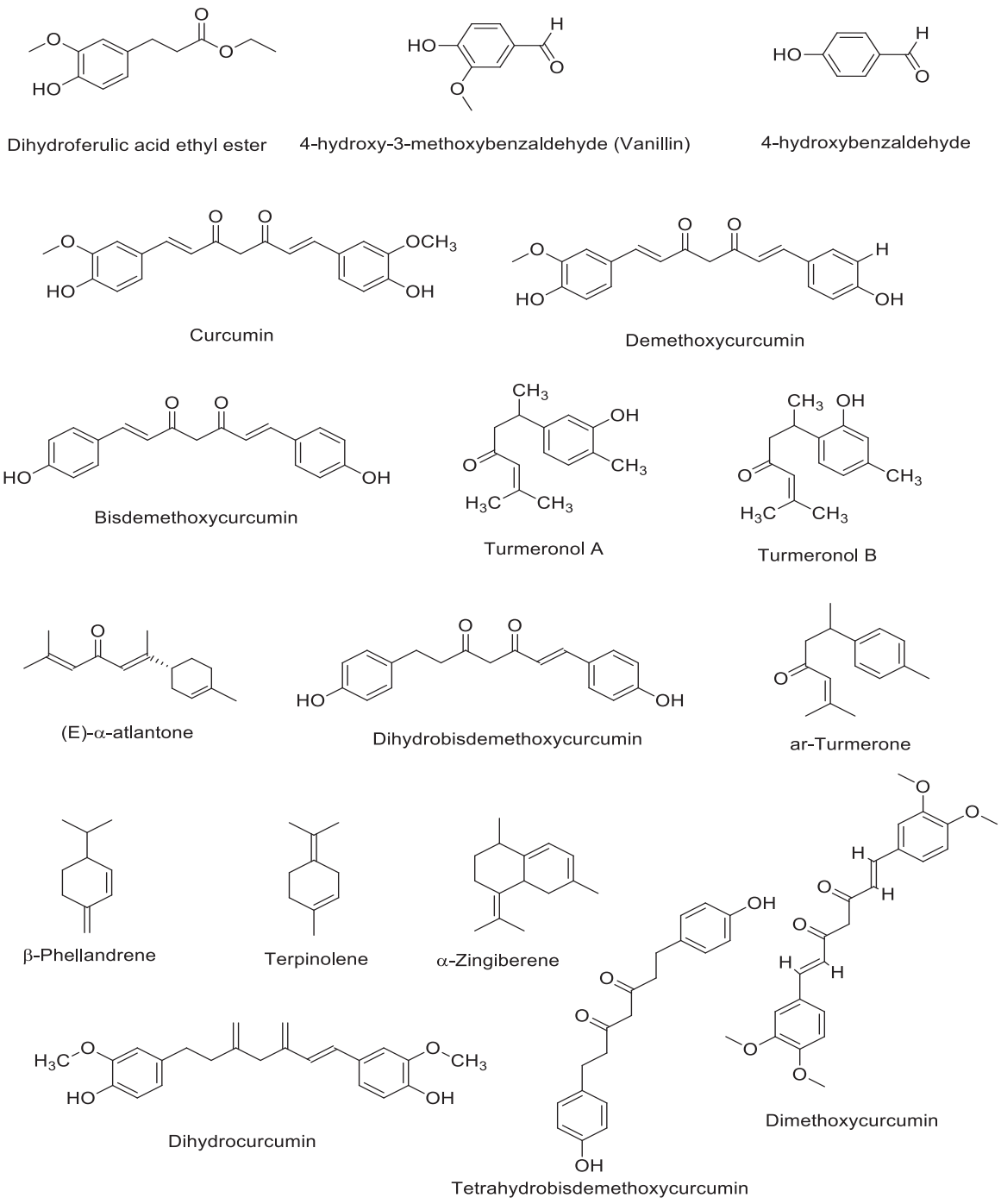

Fig. 3. Bioactive compounds isolated from *C. longa*.

acid, and ferulic acid were identified through HPLC analysis of methanol extract of *C. longa* rhizome [47]. Wang et al. [48] elucidated the chemical structure of dehydroxingeron and zingerone through spectroscopic analysis. Li et al. [49] characterized 1,7-bis-(4-hydroxyphenyl)-1,4,6-heptatrien-3-one using column chromatography and preparative HPLC of methanol extracts of *C. longa* rhizomes, as well as spectroscopic analyses, including 1D and 2D NMR.

5.2. Terpenes

Different researchers identified several terpenes, including monoterpenes and sesquiterpenes, in the plant. Spectral analyses (H NMR and C NMR) and liquid chromatography-tandem mass spectrometry (LC-MS-MS) of ethyl acetate fraction of *C. longa* powder by Akter et al. [50] identified sesquiterpenes such as turmeronol B, turmeronol A, (E)-α-atlantone, dihydrobisdemethoxycurcumin. D'Auria and Racioppi [51] also identified more sesquiterpenes, including ar-Turmerone and α-Zingiberene, using the DVB/CAR/PDMS fibre in solid phase microextraction (SPME) of *C. longa*. Similarly, the researchers also identified monoterpenes, which include β-Phellandrene and terpinolene, through the same method. Also, Abdel-lateef et al. [45] identified furanodiene and curdione using GC-MS and HPLC analysis of methanol extract of *C. longa* rhizomes and IR, H, and C NMR analysis to elucidate their chemical structures. Yuan et al. [44] identified the sesquiterpene, and bisacurone B, through spectroscopic analyses (H NMR, C NMR, HSQC, HMBC, and NOESY) of ethanol extract of *C. longa* rhizomes. Alterna-

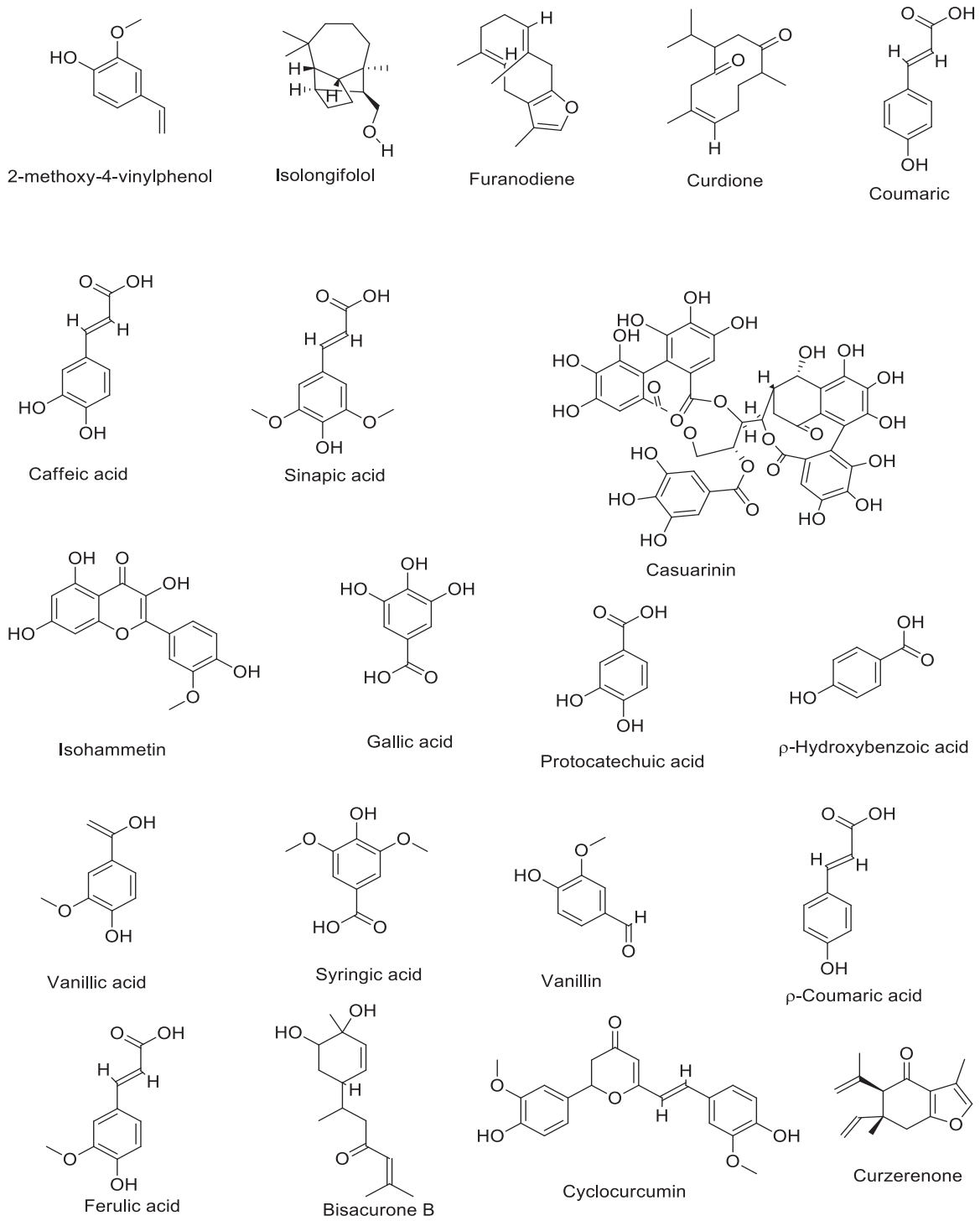

Fig. 3. Continued

tively, Wang et al. [48] further elucidated the structure of bisacurone C through spectroscopic analysis. Silica gel column chromatography and HPLC of ethyl acetate-soluble fraction of the methanol extract of *C. longa* rhizomes and NMR analysis methods were employed to identify sesquiterpenes including curzerenone, curcumenol, isocurcumenol, procurcumenol, zedoarondiol [52]. Furthermore, Lu et al. [53] identified the sesquiterpene curcumol through gas chromatography combined with surface acoustic wave sensor (GC-SAW) analysis of the *C. longa* plant. Also, through Silica gel column chromatography and preparative HPLC analysis of hexane portion obtained from methanolic extract of *C. longa* dried rhizomes, as well as advanced spectroscopic analyses (H-, C-NMR, UV, and 1R) of the plant, Lee [54] identified borneol and sabinene, which are typical monoterpenes.

5.3. Phytosterols

Phytochemical studies also revealed the presence of bioactive phytosterols. Singh et al. [35] identified three phytosterols, including stigmasterol, b-sitosterol, and stigmast-4-en-3-one, and one monoterpene, terpinene-4-ol, through GC-MS analysis of ethanol oleoresin constituents of fresh and dry *C. longa* rhizomes.

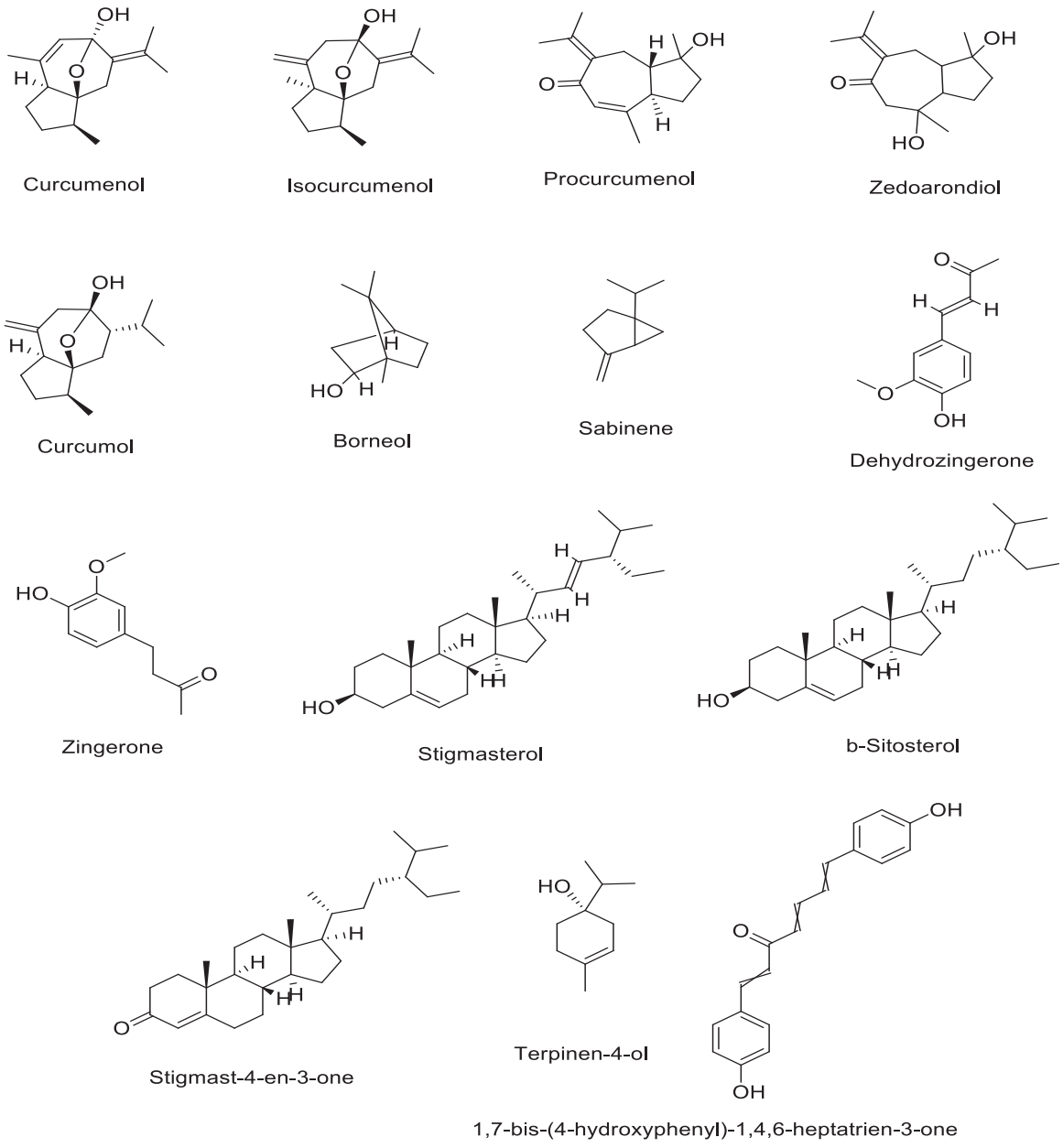

Fig. 3. Continued

5.4. Essential oils

Several bioactive essential oils were identified in different parts of *C. longa* (Fig. 4). GC-MS analysis of *C. longa* rhizomes by Jaiswal and Agrawal [55] after hydrodistillation of the fresh rhizomes using Clevenger apparatus revealed the presence of pinene, *β*-myrcene, *α*-phellandrene, p-cymene, eucalyptol, *γ*-terpinolene, *α*-terpinolene, *β*-caryophyllene, *β*-farnesene, *γ*-curcumene, ar-curcumene, zingiberene, *β*-bisabolene, *α*-santalol, *β*-atlantol, humulene epoxide, zingiberenol, ar-tumerone, curlone, tumerone, artermisia ketone, khusimone, and myrcenone. Furthermore, Xu et al. [56] identified carvotanacetone, thymol, eugenol, ylangene, *β*-cubebene, *α*-cedrene, *α*-gurjunene, aromadendrene, trans-*α*-bergamotene, (e)-*β*-farnesene, alloaromadendrene, *β*-selinene, *γ*-muurolene, *δ*-selinene, *α*-curcumene, *α*-selinene, *β*-himachalene, curzerene, valencene, *δ*-cadinene, eudesma-3,7(11)-diene, calamenene, cedrol, spathulenol, longiborneol, *β*-santalol, torreyol, *β*-eudesmol, *α*-cadinol, *α*-bisabolol, germacrone, zerumbone, (-)-drimenol, and *β*-pinene using natural deep eutectic solvents as pretreatment solvents coupled with microwave-assisted hydrodistillation (MAHD) and GC-MS analysis of leaves extract. Also, Lee et al. [57] identified limonene, citronellal, cis-*α*-bergamotene, *β*-elemene, terpinene-4-ol, *γ*-elemene, *α*-terpineol, *β*-sesquiphellandrene, geraniol, and *α*-turmerone through gas-chromatography and flame ionization detector (FID) analysis of *C. longa*. However, GC-MS/HPLC analysis of an aqueous extract of *C. longa* Radix by Chen et al. [58] revealed the presence of camphene, 3-carene, (+)−4-carene, o-cymene, 2-undecanone, humulene, nerolidol, trans-sesquisabinene hydrate, and 2-nonadecanone. Additionally, GC-MS analysis of n-hexane extract of *C. longa* rhizomes and Nuclear Magnetic Resonance (NMR) by Dias Ferreira et al. [59] identified *α*-pinene and camphor. Similarly, Kumar et al. [60] identified *α* – thujene, *α* – terpinene, *γ*-and terpinene using GC-MS analysis of hydro distillate extract of *C. longa* dried leaves. Furthermore, GC and GC-MS analysis of *C. longa* following a steam distillation and dissolution of the dried plant rhizome in DMSO by Lee et al. [61] identified trans-*β*-elemenone, 4-terpineol, 2-decanone, *δ*-elemene, *α*-humulene, trans-*β*-farnesene, linolenic acid, and linoleic

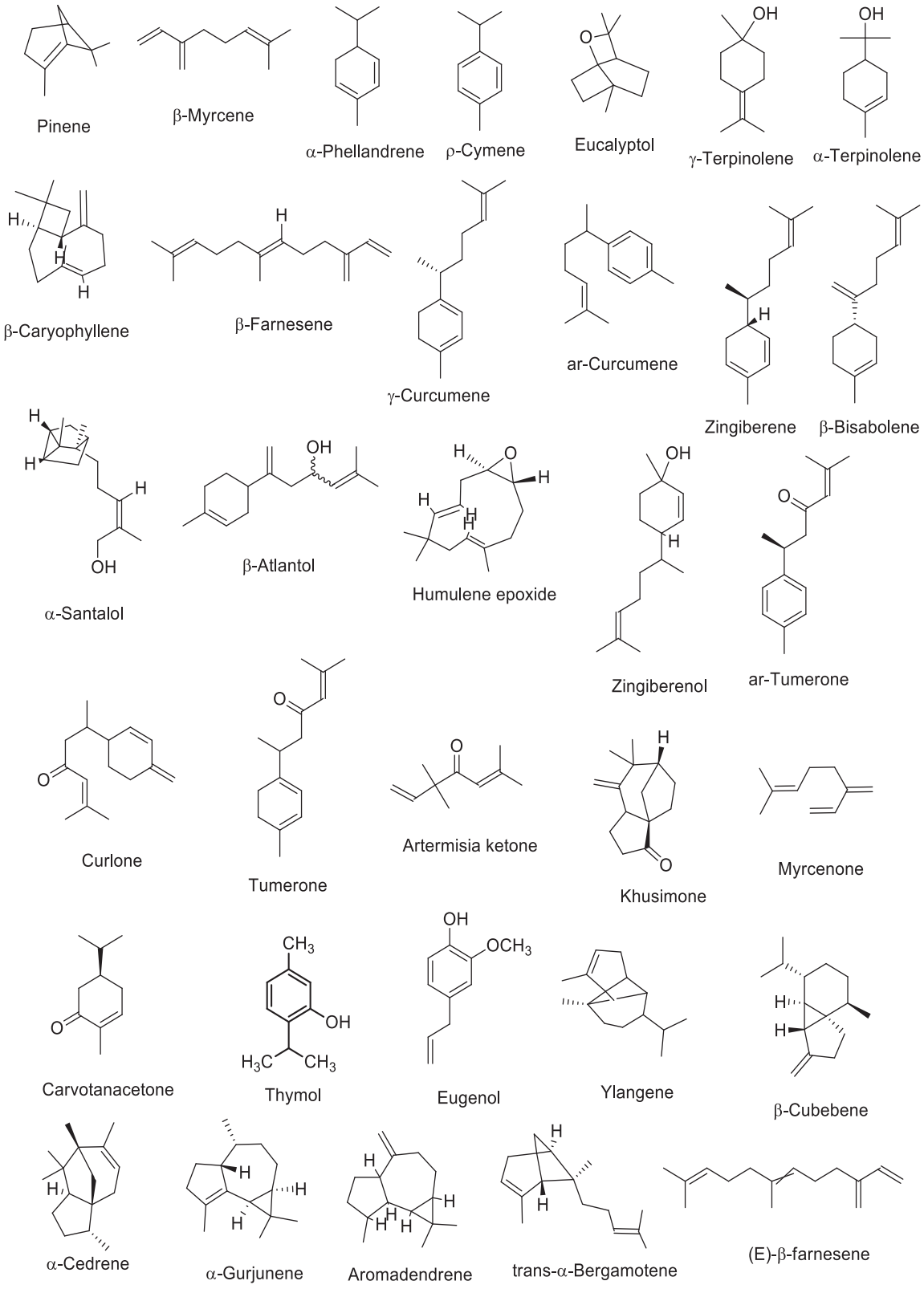

Fig. 4. Bioactive compounds isolated from essential oil of *C. longa*.

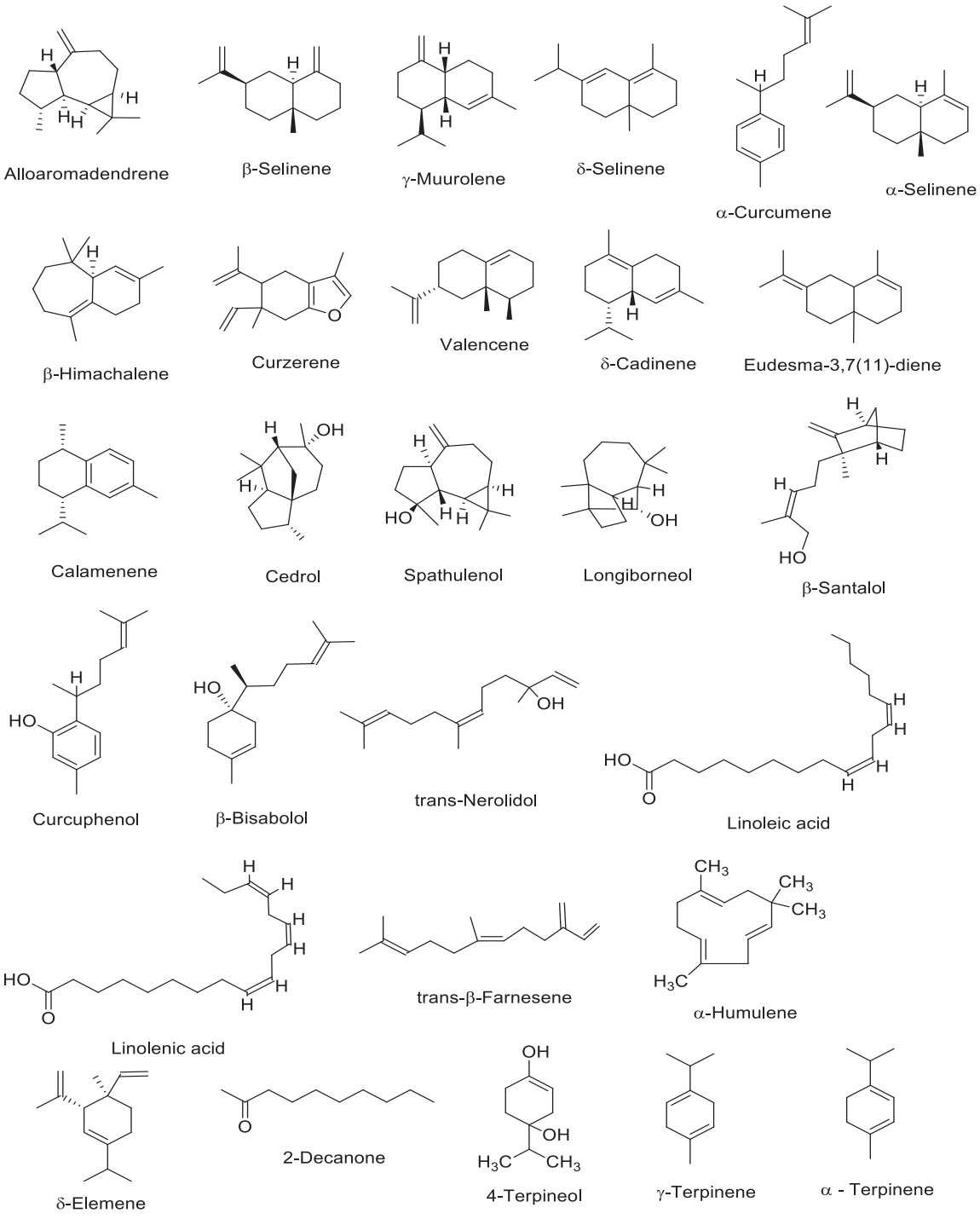

Fig. 4. Continued

acid. Singh et al. [35] conducted a GC-MS analysis of essential oil constituents of fresh and dry *C. longa* rhizomes by which trans-nerolidol, *β*-bisabolol, and curcuphenol were identified.

6. Pharmacological activity

6.1. Anti-oxidative activity

Yarru et al. [62] examined the anti-oxidative efficacy of curcumin derived from *C. longa* against aflatoxin B1 (AFB_1)-induced toxicity in broiler chicks. Broiler chicks were fed a Basal diet containing 1 mg of AFB_1, whilst chicks in treatment and control groups were treated with a diet containing 74 mg/kg of curcumin. Results from this study revealed that the administration of a curcumin-based diet attenuated AFB_1-induced superoxide dismutase (SOD), epoxide hydrolase (EH), and glutathione S-transferase (GST) genes expression in chicks (Table 1). Uzunhisarcikli and Aslanturk [13] reported the therapeutic efficacy of curcumin (100 mg kg^{-1}) in a combined dose with taurine (100 mg kg^{-1}) to ameliorate Bisphenol A-induced toxicity in rats. Curcumin showed anti-oxidative activity as it decreased MDA levels, an indicator of lipid peroxidation, whilst increasing SOD, CAT, and GPx levels. Sumanont et al. [63] studied the anti-oxidative property of curcumin

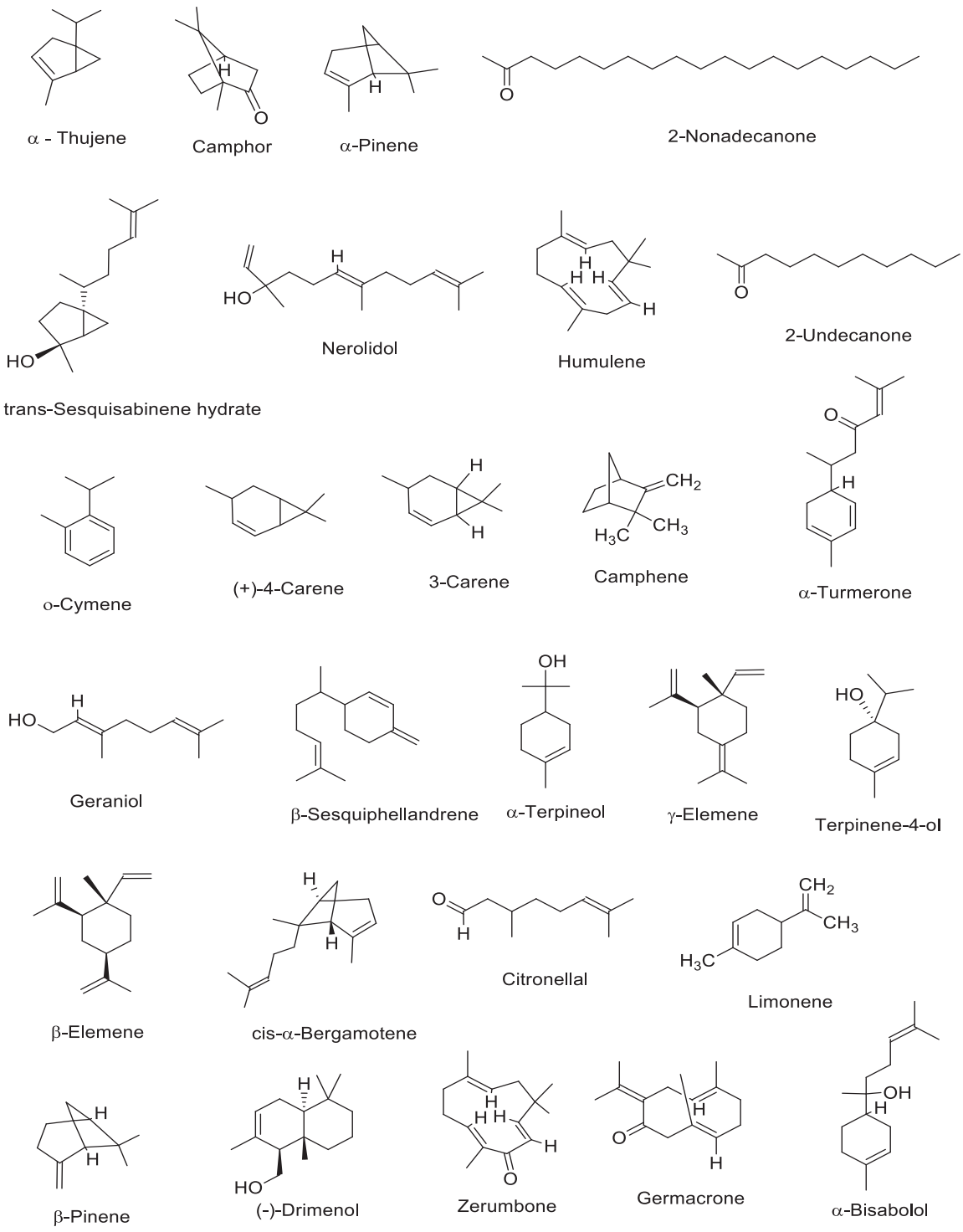

Fig. 4. Continued

and its manganese derivatives (Curcumin manganese complex (CpCpx) and diacetyl curcumin manganese complex (AcylCpCpx) by determining their nitric oxide (NO) radical scavenging ability using sodium nitroprusside generating NO system. Compounds showed IC_{50} values between 8–29 μM, emphasizing curcumin's anti-oxidative activity. In another study, Altıntoprak et al. [64] reported the anti-oxidative efficacy of curcumin against allergic rhinitis. Allergic rhinitis was induced by injecting 0.3 mg ovalbumin (OVA) dissolved in 1 mL of saline and 30 mg of aluminium hydroxide in rats. Curcumin at a 200 mg/mL dosage successfully decreased MDA levels in treatment groups (Table 1). Fujisawa et al. [65] demonstrated the anti-oxidative activity of curcumin. *In vitro* tests utilizing HSG cells showed the generation of reactive oxygen species in cells upon the administration of curcumin. 10 μM-1 mM of curcumin inhibited the polymerization of methyl methacrylate (MMA), usually initiated by peroxy radicals. Curcumin's high reactivity with peroxy radicals demonstrates chemopreventive properties. Treatment of streptozotocin-induced diabetic rats with *C. longa* and *Abroma augusta* extract resulted in decreased serum levels of cholesterol-

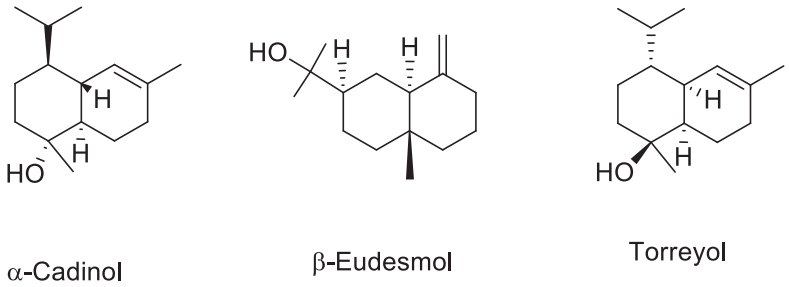

Fig. 4. Continued

abrogated lipid peroxidation [66]. Murugan and Pari [67] investigated tetrahydro curcumin, isolated from curcumin to determine its anti-oxidative efficacy. 80 mg/kg of tetrahydrocurcumin was administered in mice to treat streptozotocin–nicotinamide-induced diabetes. Findings from this study showed increased glutathione peroxidase, glutathione-S-transferase, SOD and catalase activity.

Suryanarayana et al. [68] reported that AIN-93-diets containing 0.002% or 0.01%, or 5% Turmeric reversed altered antioxidant enzyme activities induced by STZ. Curcumin also increased levels of SOD and catalase in treated rats. Yang et al. [69] utilized an ELISA assay to demonstrate the anti-oxidative properties of curcumin. Treatment of diabetic rats with curcumin at 100 and 200 mg/kg doses reduced MDA levels and elevated SOD activity. Ak and Gulcin [70] investigated the anti-oxidative activity of curcumin utilizing several techniques; DPPH, ABTS, and Fe^{3+}–Fe^{2+} transformation methods. This study showed curcumin's ability to inhibit lipid peroxidation, effective DPPH and ABTS scavenging activity and a strong reducing power on Fe^{3+} to Fe^{2+}. Findings from this study revealed curcumin's inhibition of 97.3% lipid peroxidation of linoleic acid emulsion at a dosage of 15 μg/mL, compared to 95.4, 99.7, 84.6 and 95.6% from standard antioxidants (butylated hydroxyanisole, butylated hydroxytoluene, α-tocopherol and Trolox respectively). Curcumin also showed efficient DPPH, ABTS scavenging activity and ferric ions (Fe^{3+}) reducing power. Barzegar and Moosavi-Movahedi [71] performed *in vitro* tests to determine curcumin anti-oxidative activity against L-6 myoblasts cells exposed to cumene hydroperoxide. The authors reported that curcumin inhibited cell ROS production and suppressed intracellular fluorescence intensity. Sreejayan and Rao [72] reported curcumin's vigorous scavenging activity against nitric oxide generated from sodium nitroprusside. Gao et al. [73] revealed that curcumin protected the liver from arsenic-induced hepatotoxicity in rats. Hepatic malonaldehyde (MDA) levels were restored to healthy levels in treatment groups. Further results showed an increase in GSH levels. Curcumin reduced antioxidant biomarkers to similar levels to the control groups [14].

Girish and Pradhan [74] tested the anti-oxidative efficacy of different phytochemicals, curcumin, picroliv, and ellagic acid, against CCl_4-induced toxicity in rats using silymarin as a standard drug. Pretreatment of rats with the phytochemicals reduced elevated MDA levels to similar levels to that of silymarin whilst also increasing GSH levels. Namgyal et al. [75] reported that curcumin restored SOD, catalase and GSH activity and protected against cadmium-induced toxicity in rats. Further reports showed that curcumin significantly decreased MDA levels indicating good anti-oxidative activity (Table 1). Liu et al. [76] carried out *in vitro* experimental examination to determine the anti-oxidative effect of curcuminoids derived from the rhizome of *C. longa*. Advanced glycation end products (AGEs)-induced apoptotic HBZY-1 cells were treated with different doses of curcumin and demethoxycurcumin (10^{-9}, 10^{-10} and 10^{-11} M) curcumin. Results from this study revealed that the administration of the extract restored SOD activity and decreased MDA levels in treated cells. Fernández-Marín et al. [77] utilized DPPH, FRAP and ABTS assays to determine and compare the anti-oxidative potency between microwave-assisted extracted (MAE) *C. longa* oil and Soxhlet-extracted *C. longa* oil. ABTS assay results showed that phenolic compounds in (MAE) *C. longa* oil improve its anti-oxidative efficacy. Reddy and Lokesh [78] reported that a diet containing 1% turmeric had an anti-oxidative effect on rats injected with 30 mg of ferrous sulphate.

6.2. Hepatoprotective activity

Zhai et al. [79] examined the hepatoprotective effect of curcumin extracted from the rhizome of *C. longa* against ochratoxin A-induced toxicity in white Pekin ducklings. 400 mg/kg of curcumin decreased serum LDL levels and increased liver catalase levels. Lee et al. [14] investigated the protective effect of curcumin and *C. longa* extract against CCl_4-induced toxicity and observed a significant decrease in serum ALT and AST levels. In a similar study, Sengupta et al. [80] studied the effect of *C. longa* extract treatment on CCL_4-induced toxic rats. Administration of extract decreased AST, ALT and bilirubin levels.

Further studies revealed the inhibition of morphological changes, phagocytosis and release of nitric oxide. In another study, Banji et al. [81] reported the hepatoprotective effect of curcumin in rats injected with Freund's Complete Adjuvant (CFA). Curcumin reportedly reduced AST, ALT, ALP and bilirubin levels in the liver of rats in treatment groups. Treatment of rats with 200 mg/kg of thioacetamide (TAA) with 300 mg/kg of curcumin demonstrated the hepatoprotective effect of curcumin. Curcumin inhibited nodule formation and decreased hydroxyproline levels [82]. Rats treated with 200 mg/kg of curcumin reduced arsenic and elevated AST and ALT levels [73]. Joshi et al. [83] examined the therapeutic effect of curcumin and *C. longa* extract against mercuric chloride ($HgCl_2$)-induced toxicity in rats. Rats were administered 200 mg/kg of *C. longa* and 80 mg/kg of curcumin for three days. Rats were sacrificed after 24 h, and administration of extracts reversed the increase in AST, bilirubin, GGT, ALP, ALT and LDH enzyme activities. Girish and Pradhan [74] reported the hepatoprotective effect of curcumin on CCl_4-induced toxic rats in combination with picroliv and ellagic acid. Assessment of liver enzymes revealed reduced ATP, AST and ALP serum levels. Curcumin also suppressed hepatic necrotic damage. Farombi et al. [84] studied the hepatoprotective effect of curcumin on Dimethylnitrosamine-induced toxicity in mice. Mice in treatment groups were pre-treated with 200 mg/kg of curcumin for four consecutive days. This study revealed elevated liver haem oxygenase (HO)−1 protein expression, activated Nrf2 expression and increased antioxidant response element (ARE)-binding activity. Curcumin ameliorated induced Aflatoxin B1-induced liver lesions and oxidative stress in broilers [85]. Gutierres et al. [86] demonstrated the hepatoprotective potency of curcumin against STZ-diabetic rats. Treatment of rats with curcumin combined in yoghurt reduced liver enzymes AST and ALT (Table 1).

6.3. Antidiabetic activity

Essa et al. [20] showed that the administration of different doses of curcumin significantly reduced the serum glucose levels of STZ-induced diabetic rats. Eshrat and Hussain [66] examined the co-administration of

Table 1
Pharmacological activities of *C. longa*.

Doses	Experimental models	Observation	Effects	References
74 mg/kg of curcumin	1 mg of aflatoxin B_1 (AFB1) inoculated in 80 male broiler chicks	Attenuated AFB_1 decreased SOD, epoxide hydrolase, and GSTα gene expression. Extracts increased GPx genes levels	Anti-oxidative activity	[62]
Combined dose of 100 mg/kg curcumin and taurine	130 mg/kg of Bisphenol A (BPA) administered in Wister rats	Increased levels of SOD, CAT, GPx, and GST whilst decreasing MDA levels	Anti-oxidative activity	[13]
Different concentrations of curcumin, diacetylcurcumin, curcumin manganese complex (CpCpx), diacetylcurcumin manganese complex (AcylCpCpx)	10 mM of sodium nitroprusside	Complexes showed higher scavenging activity with significantly lower IC_{50} values.	Anti-oxidative activity	[63]
200 mg/mL of curcumin	Rats	Increased serum SOD, paraoxonase and arylesterase levels but decreased MDA levels	Antioxidative activity	[64]
10 μM-1 mM of curcumin and related compounds	5×10^3 HSG cells	Produced ROS in cells and revealed the longest induction period against peroxy radicals compared to other tested compounds	Anti-oxidative activity	[65]
300 mg/kg of aqueous *Curcuma longa* and *Abroma augusta* extract	60 mg/kg of STZ in rats	Decreased serum levels of cholesterol and inhibited lipid peroxidation. Also increased SOD and CAT activity	Anti-oxidative activity	[66]
80 mg/kg of tetrahydrocurcumin	65 mg/kg of STZ in rats	Increased glutathione peroxidase, glutathione-S-transferase, SOD and catalase activity whilst reducing glutathione level	Anti-oxidative activity	[67]
AIN-93 diet containing 0.002% or 0.01% curcumin	35 mg/kg of STZ injected into rats	Increased SOD and CAT levels in specific organs, whilst GPx activity decreased	Anti-oxidative activity	[87]
50 mg/kg of curcumin	A single dose of 55 mg/kg STZ in rats	Decreased level of thiobarbituric acid-reacting substances and attenuated SOD decrease	Anti-oxidative activity	[87]
100, 200 mg/kg of curcumin	40 mg/kg of STZ and a high-fat diet in rats	Decreased MDA levels and elevated SOD activity. Curcumin also inhibited retina apoptosis	Anti-oxidative activity	[90]
0–45 μg/mL of curcumin	Linoleic acid emulsion system	Curcumin showed significant antioxidant potential against lipid peroxidation and strong reducing power on Fe^{3+} to Fe^{2+}	Anti-oxidative activity	[70]
10,20 and 40 μM of curcumin	L-6 myoblasts cells exposed to cumene hydroperoxide	Suppressed intracellular fluorescence intensity and inhibited ROS production	Anti-oxidative activity	[71]
Different concentrations of curcumin	Nitric oxide generated from sodium nitroprusside	25 μM of curcumin reduced produced nitrite; curcumin also scavenged produced nitric oxide	Anti-oxidative activity	[72]
200 mg/kg of curcumin	10, 50 and 100 mg/L of arsenic administered to rats	Attenuated induced increase in MDA and reversed reduced blood GSH levels	Anti-oxidative activity	[73]
100, 200, or 300 mg/kg of *C. longa* extract and 200 mg/kg of curcumin	0.1 mL/100 g of carbon tetrachloride (CCl_4) in rats for 3 days	Inhibited ROS production and lipid peroxidation	Anti-oxidative activity	[14]
50 and 100 mg/kg of curcumin, picroliv, ellagic acid	1 mg/kg of (CCl_4) in rats	Restored elevated MDA levels and increased GSH levels	Anti-oxidative activity	[74]
20,40,80 and 160 mg/kg of curcumin	2.5 mg/kg of cadmium administered in rats	Decreased MDA levels whilst SOD, catalase and GSH activity increased	Anti-oxidative activity	[75]
10^{-9}, 10^{-10} and 10^{-11} M of curcumin and demethoxycurcumin	Advanced glycation end products (AGEs)-induced apoptotic HBZY-1 cell	Attenuated reduced SOD activity and decreased MDA levels.	Anti-oxidative activity	[76]
Microwave-Assisted extracted (MAE) and Soxhlet extracted *C. longa* oil	DPPH, FRAP and ABTS assay	ABTS assay showed best results with MAE sample containing more phenolic components	Antioxidative activity	[77]
Diet containing 1% turmeric	30 mg of ferrous sulphate injected into rats	Increased SOD, catalase and glutathione peroxidase activity	Anti-oxidative activity	[78]
400 mg/kg of curcumin	2 mg/kg of ochratoxin A administered in White Pekin ducklings	Curcumin decreased serum LDL levels and increased liver CAT activity	Hepatoprotective activity	**Zhai et al. (2009)**
100, 200, or 300 mg/kg of *C. longa* extract and 200 mg/kg of curcumin	0.1 mL/100 g of carbon tetrachloride (CCl_4) in rats for 3 days	Significant decrease in serum ALT and AST levels	Hepatoprotective activity	[14]
50 mg/kg of aqueous *Curcuma longa* extract	0.5 mL/kg of carbon tetrachloride injected into mice	Decreased SGOT, SGPT and bilirubin. Also, ameliorated induced morphological changes	Hepatoprotective activity	[80]
30,100 mg/kg of curcumin and 1 mg/kg of methotrexate	0.1 ml of Freund's Complete Adjuvant (CFA) in rats	Decreased SGOT, SGPT, ALP and bilirubin levels	Hepatoprotective activity	[81]
300 mg/kg of curcumin	200 mg/kg of thioacetamide (TAA) in rats	Inhibited nodule formation and decreased hydroxyproline levels. Also, inhibited hepatic stellate cells and the absence of collagen αI	Hepatoprotective activity	[82]
200 mg/kg of curcumin	10, 50 and 100 mg/L of arsenic administered to rats	Ameliorated increased AST and ALT levels	Hepatoprotective activity	[73]
200 mg/kg of *C. longa* and 80 mg/kg of curcumin	A single dose of 12 μ/mol/kg of mercuric chloride ($HgCl_2$) administered in rats	Reversed increase in AST, bilirubin, GGT, SALP, ALT and LDH enzymes activities	Hepatoprotective activity	[83]
50 mg/kg of curcumin, picroliv, ellagic acid	1 mg/kg of carbon tetrachloride (CCl_4) in rats	Reduced serum levels of ATP, AST and ALP. Curcumin also suppressed hepatic necrotic damage	Hepatoprotective activity	[74]
200 mg/kg of curcumin	20 mg/kg of Dimethylnitrosamine in mice	Elevated liver haem oxygenase (HO)−1 protein expression, activated Nrf2 expression and increased antioxidant response element (ARE)-binding activity	Hepatoprotective activity	[84]

(*continued on next page*)

Table 1 (*continued*)

Doses	Experimental models	Observation	Effects	References
300 mg/kg of curcumin	1 mg/kg of Aflatoxin B1 in diet administered to broilers	Ameliorated liver damage, increased liver GSH and SOD activity	Hepatoprotective activity	[85]
30,60 and 90 mg/kg of curcumin in yoghurt	40 mg/kg of STZ in rats	Dose-dependant decrease in AST and ALT levels	Hepatoprotective activity	[86]
100, 250 and 500 mg/kg of curcumin	75 mg/kg of streptozotocin (STZ) injected in mice	Significant reduction in serum glucose levels	Antidiabetic activity	[20]
300 mg/kg of aqueous *C. longa* and *Abroma augusta* extract	60 mg/kg of STZ in rats	Reduced fasting plasma glucose levels in treated rats	Antidiabetic activity	[149]
50 mg/kg of curcumin	Single dose of 55 mg/kg STZ in rats	Reduced blood urea nitrogen levels and ameliorated decrease in albumin	Antidiabetic activity (nephropathy)	[87]
Diet containing 0.5% curcumin	60 mg/kg of STZ in rats	Decreased kidney weight, lessened leaching of glucose-6-phosphatase, LDH, AST and acid phosphatase. Curcumin also increased ATPase activity and decreased ALT and ALP levels	Antidiabetic activity (nephropathy)	[88]
100 mg/kg of curcumin	55 mg/kg of STZ in rats	Reduced PKC-α and PKC-β1 expressions also, inhibited phosphorylation of p44/p42 ERK and VEG F expression	Antidiabetic activity	[105]
150 mg/kg of curcumin	65 mg/kg of STZ in rats	Downregulated expression of endothelial nitric oxide synthase and endothelin-1 and transforming growth factor-β1 in kidney	Antidiabetic activity	[89]
100, 200 mg/kg of curcumin	40 mg/kg of STZ and a high-fat diet in rats	Increased body weight and decreased blood glucose level. Also observed was the improved thickness of the retina	Antidiabetic activity	[90]
30,60 and 90 mg/kg of curcumin in yoghurt	40 mg/kg of STZ in rats	Reduced blood glucose level, highest dose reduced level of proteinuria	Antidiabetic activity	[86]
10 mM; 100 μl/mouse of curcumin and 10^6 of bone marrow transplantation	40 mg/kg of STZ in rats	Reduced blood glucose levels and increased glucose clearance. Also, observed was ameliorated reduced insulin levels	Antidiabetic activity	[91]
0.2 or 1.0 g/100 g of ethanol *C. longa* extracted diet	Diabetic KK-A^y/Ta mice	Suppressed glucose increase	Antidiabetic activity	[92]
80 mg/kg of tetrahydrocurcumin	65 mg/kg of STZ in rats	Decreased glucose levels and elevated plasma insulin levels	Antidiabetic activity	[67]
3 units of insulin and 150, 200 and 250 mg/kg of *C. longa* dissolved in milk	Different doses of 45 and 65 mg/kg STZ in rats	Lowered blood glucose level and 27.9% fall in glucose tolerance study at 200 mg/kg	Antidiabetic activity	[93]
15 or 30 mg/kg of curcumin	65 mg/kg of STZ in rats	Reduced plasma glucose level, ameliorated weight loss, decreased diabetic proteinuria, polyuria and elevated levels of serum creatinine and blood urea nitrogen	Antidiabetic activity (nephropathy)	[94]
50 mg/kg of curcumin	1 mg of zymosan injected in rats	Increased Col2, SOX-5 expression and chondrocytes number	Anti- Osteoarthritis activity	[15]
10–11 M of IL-1beta and 5–20 μM Curcumin	Chondrocytes from human articular cartilage and human cartilage explants from Osteoarthritic patients	Inhibited PGE_2, basal IL-6, IL-8 and MMP3 production, NO synthesis	Anti- Osteoarthritis activity	[95]
1 and 8 mg/kg of prednisone and 100 mg/kg of curcumin	0.05 mL zymosan in knees of rats	Attenuated reduced number of neutrophils and reduced joint inflammation	Anti-arthritis activity	[18]
200 mg/kg of turmeric or ginger rhizomes powder	0.1 ml of CFA in the paw of rats	Suppressed paw swelling and ameliorated body weight loss. Reverted increased leucocyte, granulocyte and agranulocyte Counts	Anti-arthritis activity	[72]
5–15 μM of curcumin or 8–14 μM of α-mangostin	18 μM of Iodoacetate exposed to cerebellar granule neurons (CGNs) obtained from neonatal rats	Inhibited reactive oxygen species formation, attenuated induced cell death and enhanced HO-1 expression	Neuroprotective activity	[97]
100,200 and 300 mg/kg of ethanolic turmeric extract	8 mg/kg of trimethyltin injected in mice	Increased Brain SOD, CAT and GSH levels. Also, decreased MDA levels	Neuroprotective activity	[98]
0.001, 0.01, 0.05, 0.1, 0.2 and 0.4 mg/ml of *C. longa*	SH-SY5Y cells	Reduced cell viability and distorted morphology. Extract also induced apoptosis and generated reactive oxygen species	Neuroprotective activity	[99]
100 and 300 mg/kg of curcumin	ischaemia injured rats	Reduced brain water, ameliorated nerve damage, decreased cerebral infarct volume and lessened abnormal cells	Neuroprotective activity	[19]
10 mg/kg of curcumin-loaded lipid core nanocapsules and 50 mg/kg of curcumin	β-amyloid1–42 ($A\beta_{1-42}$) injected in mice	Ameliorated elevated mRNA expression of IL-6, NF-κB, TNF-α and IL-1β	Neuroprotective activity	[100]
2 μM sol of curcumin and nanocurcumin	rotenone-induced neurotoxic SK-N-SH cells	Reduced release of lactate dehydrogenase and preserved cell morphology in treated cells. Nano curcumin decreased ROS levels	Neuroprotective activity	[101]
20,40,80 and 160 mg/kg of curcumin	2.5 mg/kg of cadmium administered in rats	Improved locomotor activity, recognition memory and spatial learning lowered stress and anxiety levels	Neuroprotective activity	[75]
0.001, 0.01, 0.05, 0.1, 0.2 and 0.4 mg/ml of *C. longa* extract	Salsolinol-treated SH-SY5Y cells	Ameliorated cell growth inhibition, normal morphological arrangements, reduced ROS generation, decreased p53, Bcl-2 and caspase-3 levels	Neuroprotective activity	[99]

(*continued on next page*)

Table 1 (*continued*)

Doses	Experimental models	Observation	Effects	References
100 mg/kg of *C. longa*	20 mg/kg of Cerium chloride ($CeCl_3$) in mice	Decreased number of cases crossed in OF test and increased number of entries in open arms	Neuroprotective activity	[102]
25,50,100 and 300 mg/kg of Curcumin	0.1 ml of 2,4,6-trinitrobenzene sulphonic acid (TNBS) injected in mice	Inhibited colon and spleen weight gain. Also reduced colon NO and O_2^-levels	Anti-inflammatory activity	[103]
1–1000 μM of curcumin	3T3-L1 fibroblasts cells	Inhibited NF-κB activation and suppressed gene expression of TNF-α, IL-1β, IL-6, and COX-2	Anti-inflammatory activity	[104]
100 mg/kg of curcumin	55 mg/kg of STZ injected in mice	Suppressed TNF-α, TGF-β1, ICAM-1, MCP-1, and IL-1β expression levels. Also, it inhibited NF-κB activation and IκBα degradation	Anti-inflammatory activity	[105]
50 mg/kg of curcumin and doses of curcumin nano-emulsions	0.1 mL of CFA in rats	Decreased TNF-α and IL-1β levels and reduced spleen and thymus weight indices. Also, extract attenuated inflammatory cell infiltration	Anti-inflammatory activity	[106]
0.1% of aqueous *C. longa* and 2% *Berberis aristata* extract	20 μL of the endotoxin (lipopolysaccharide from *E. coli*) in rabbits	Reduced inflamed cell count and decreased TNF-α level	Anti-inflammatory activity	[107]
400μl of Pluronic F-127 and 400μl of curcumin	60 mg/kg of STZ administered to wounded rats	Faster wound contraction, decreased TNF-α mRNA, IL-1β and MMP-9 expressions; however, IL-10 mRNA levels increased	Anti-inflammatory activity	[108]
300 μg of curcumin	50 μg chicken egg ovalbumin (OVA) in 1 mg alum injected in BALB/c mice	Inhibited diarrhoea, mastocytosis, OVA-IgE and intestinal oedema production	Anti-inflammatory activity	[16]
50 μM of curcumin	Chondrocytes treated with 10 ng/mL IL-1β	Downregulated MMP-3, ameliorated decrease in type II collagen	Anti-inflammatory activity	[109]
25- 300 mg/kg of curcumin	0.1 ml of 2,4,6-trinitrobenzene sulphonic acid in mice	Prevented damage to the large intestine and prevented an increase in NO & $O2^-$ levels and malondialdehyde levels	Anti-inflammatory activity	[103]
5,10,20μmol/L of curcumin	3T3-L1 adipocytes treated with 0.25 mmol/L palmitate	Elevated uptake of insulin-stimulated 2-deoxyglucose, downregulated TNF-α and IL-6 expression	Anti-inflammatory activity	[48]
0,5,10, 20μmol/L of curcumin	3T3-L1 cell lines	Reduced VEGFα expression and inhibited angiogenesis	Anti-obesity activity	[111]
500 mg/kg of curcumin	C57BL/6 mice fed high fat; AIN-93 diet	Suppressed body weight gain, inhibited hepatic steatosis. Also, reduction in VEGF mRNA and VEGFR-2 gene expression	Anti-obesity activity	[111]
0–60 μM of curcumin	PC-14, p34, H1299 and Panc-1 cell lines	Decreased COX-2 and EGFR expression and inhibited Erk1/2 activity	Anticancer activity	[112]
0–40μMol of curcumin	MCF-7 and MDA-MB-231 cells	Reduced cell viability and increased p27 and p21 expression. Also, inhibition of Akt phosphorylation was observed	Anticancer activity	[17]
50μmol/L of curcumin	MDA-MB-435 cells	Inhibited NF- κB, IκBα activation and phosphorylation. Also, Induced apoptosis and decreased antiapoptotic protein expression	Anticancer activity	[113]
0–100 μM of curcumin	MCF-7 cells	Decreased cell viability, distorted morphological arrangements, induced apoptosis, elevated cleaved PARP	Anticancer activity	[114]
25 μM of curcumin	MDA-MB-231cells	Induced apoptosis, reduced cell viability, suppressed NF-κB activation and MMP-1& MMP-2 mRNA	Anticancer activity	[115]
0–60 μM of curcumin	MCF-10F cells, malignant cell lines	Inhibited colony formation, altered cell cycle progression, decreased Rho-A protein expression and enhanced cleaved PARP-1 expression	Anticancer activity	[116]
100,200,300,400 mg/kg of curcumin	Middle cerebral artery occlusion (MCAO) surgery in mice	Ameliorated morphological alterations and decreased infarct volume	Anticancer activity	[117]
0–16 μM of curcumin	SAS, OC3, OECM-1 cells and NHOKs	Increased IGFBP-5 mRNA expression and elevated C/EBPα binding to the IGFBP-5 promoter	Anticancer activity	[118]
5–60 μM of curcumin	HeLa, SiHa, and C33A cells	Inhibited cell proliferation, induced apoptosis and DNA fragmentation. Also, HPV 16 E6 and E7 expressions level decreased	Anticancer activity	[119]
A diet containing 2% of curcumin	1×10^6 of LNCaP cells injected in mice	Suppressed cell proliferation and induced apoptosis	Anticancer activity	[120]
0–0.15 mM of curcumin	purified protein kinase A (PkA), protein kinase C (PkC), protamine kinase (cPK), phosphorylase kinase (PhK), autophosphorylation-activated protein kinase (AK) and $pp60^{c\text{-}src}$ tyrosine kinase	Inhibited kinase activity	Anticancer activity	[78]
0–70 μM/l of curcumin	MCF-10F, Tumor2 and MDA-MB-231	Inhibited cell proliferation, increased expression of specific genes and delayed cell cycle progression	Anticancer activity	[121]
Combined curcumin (50 mg/kg) and oxaliplatin (25 mg/kg) dose	1×10^6 LoVo cells injected in mice	Combine dose inhibited cancer growth; cells displayed apoptotic characteristics and increased cell population in S and G2/M phases	Anticancer activity	[122]

(*continued on next page*)

Table 1 (*continued*)

Doses	Experimental models	Observation	Effects	References
0–50 μM of curcumin	MCF-7 and MDA-MB-231 cells	Inhibited cell proliferation and suppressed pS2 and TGF-α, and ER transcript levels. Curcumin also downregulated VEGF, MMP-2 and b-FGF	Anticancer activity	[123]
Diet containing 1% curcumin	5×10^5 PC-3 cells injected in mice	Inhibited lung metastasis	Anticancer activity	[124]
5,10,20 and 40 μM of curcumin	NCL-H460, BEAS-2E and A549 cells	Induced apoptosis, elevated caspase-3 activity and inhibited cell proliferation. Upregulated miR-192–5p expression and inhibited PI3K/Akt signalling pathway	Anticancer activity	[125]
5, 10, 25, and 50 μM of curcumin	MDA-MB-231 cells	Suppressed cell proliferation, decreased Akt expression and p62 protein level, although LC3-II expression increased	Anticancer activity	[126]
5–200 μM of curcumin or 0.1 – 100 nM of rapamycin	SKN cells	Both compounds inhibited cell growth and suppressed phosphorylation of mTOR, p70S6 and S6 ribosomal proteins. Curcumin also increased cleaved PARP and caspase-3 activity	Anticancer activity	[127]
Diet containing 500 ppm curcumin	0.5 mg/kg of N-nitrosomethylbenzylamine (NMBA) injected in male F344 rats	Reduced incidence and multiplicity of oesophagal neoplasms and inhibited biomarkers of cell proliferation	Anticancer activity	[128]
0–50μmol/L of curcumin	A549 cells	Inhibited cell growth, induced apoptosis and downregulated miR-186 expression	Anticancer activity	[129]
25 mg/kg of curcumin	*Helicobacter pylori* injected in mice	Eliminated *H. pylori* from the stomach of mice	Anti-microbial activity	[131]
20–120 μM of curcumin	*Bacillus subtilis* 168, *E. coli* BL21, *E. coli* K12 MG1655	Inhibited bacterial growth and formation of Z rings, induced filamentation,	Anti-microbial activity	[93]
1024–0.5 μg/mL of *curcuma longa* fractions and antibiotics	*Staphylococcus aureus, B. subtilis, E. coli, Pseudomonas aeruginosa, and V. cholerae*	A combined dose of extract and antibiotic revealed reduced MIC values. Also reduced bacterial count	Anti-microbial activity	[22]
0.5 mg/mL of curcumin	10^8 of *Campylobacter jejuni* injected in IL-$10^{-/-}$ mice	Curcumin attenuated *C. jejuni* increased permeability and conductance to fluorescein	Anti-microbial activity	[132]
200 and 500 mg/L of *C. longa* extract	HepG2 cells and HepG 2.2.15 cells	Inhibited secretion of HBsAg and decreased HBV viral DNAs. The extract also increased p53 mRNA expression	Anti-microbial activity	[133]
The concentration of curcumin and α-methyl cinnamaldehyde (MCD)	38 isolates of *Candida* strains	Exhibited 90% growth inhibition of fungi and induced haemolysis	Anti-microbial activity	[130]
Different fractions of *C. longa* extract	*Pyricularia grisea, R. solani, Botrytis cinerea, P. infestans* cultured on potato dextrose agar	Curcumin showed significant fungicidal activity against tested bacteria	Anti-microbial activity	[134]
0.25,0.5 and 1 mg of ethyl acetate, methanol and water extract of *C. longa*	13 clinical isolates of staphylococcal strains	Inhibited microbial growth and MRSA invasion of human mucosal fibroblasts	Anti-microbial activity	[133]
0.5–256 mg/L of curcumin	23 fungi strains	Suppressed growth of *Paracoccidioides brasiliensis* and inhibited adhesion of *Candida* species	Anti-microbial activity	[135]
5–15 mM curcumin	Huh7/Rep-Feo and Huh7 cells	Inhibited HCV replicon replication, decreased levels of HCV NS5A protein	Anti-microbial activity	[136]
25 or 50 mg/kg of curcumin	SS1 or AM1 *H. pylori* cells injected in mice	Eliminated mucosal damage, eradicated *H. pylori* cells and suppressed MMP-9 activity	Anti-microbial activity	[137]
Concentrations of curcumin	10 *S. aureus* strains containing four methicillin-resistant *S. aureus*	Showed MIC values between 125 and 250 μg/ml reducing bacterial count and improved antibiotic efficacy	Anti-microbial activity	[138]
25, 50 and 100 μM of curcumin I	*S. aureus, Enterococcus faecalis, E. coli and Pseudomonas aeruginosa*	Increased killing of bacteria and increased Propidium iodide fluorescence intensity	Anti-microbial activity	[139]
25 μM of curcumin	Cardiac fibroblasts isolated from rats	Reduced cell migration and proliferation. Also, it inhibited Akt phosphorylation and Increased MMP-2 activity	Cardioprotective activity	[140]
100 and 300 mg/kg of curcumin	50 mg/kg of 5-fluorouracil injected in mice	Downregulated expression of CXCL1 and CXCL2 genes	Antidiarrheal activity	[21]
100 mg/kg of curcumin	75 mg/kg of Irinotecan (CPT-11) injected in BALB/c	Increased body weight and energy. Reduced frequency of stool and reversed intestinal mucosa damage	Antidiarrheal activity	[141]

aqueous extracts of *C. longa* and *Abroma augusta* to determine the antidiabetic potency. Diabetes was induced in rats by administering 60 mg/kg of STZ. Administration of extract significantly reduced fasting plasma glucose levels. Tikoo et al. [87] examined curcumin's lowering effect on blood urea nitrogen levels in diabetic rats to prevent nephropathy. Findings from this study showed that the administration of 55 mg/kg of STZ resulted in increased creatinine and blood urea nitrogen levels. Babu and Srinivasan [88] investigated the antidiabetic efficacy of curcumin against STZ-induced diabetes in rats. Rats in treatment groups were fed a diet containing 0.5% curcumin for eight weeks. Examination of kidney enzymes revealed the reduction of glucose-6-phosphatase, LDH, AST and acid phosphatase. Curcumin also reversed the increased AST and ALT levels. Another study revealed that curcumin is involved in antidiabetic treatment through the downregulation of endothelial nitric oxide synthase, endothelin-1 and transforming growth factor-β1 in the kidney of STZ-induced diabetic rats [89].

Yang et al. [90] reported the anti-hyperglycemic effect of curcumin against STZ-induced diabetes through curcumin treatment. Sixteen weeks of administration of curcumin in rats abrogated diabetes-induced retina effects and lowered blood glucose. Curcumin supplemen-

tation (30, 60 and 90 mg/kg) combined with yoghurt reduced blood glucose levels and reduced the level of proteinuria in STZ-induced diabetic rats [86]. El-Azab et al. [91] reported the treatment of STZ-induced diabetic rats with 10 mM of curcumin and 106 bone marrow transplantation. Results showed reduced blood glucose levels and increased glucose clearance (Table 1). Treatment also ameliorated reduced insulin levels. Kuroda et al. [92] demonstrated the antidiabetic efficacy of ethanolic *C. longa* extract on diabetic KK-A^y/Ta mice. EtOH extract maintained blood glucose at an appropriate level preventing diabetes mellitus 2. The administration of tetrahydrocurcumin, a curcumin derivative in STZ-induced diabetic rats, decreased glucose levels and elevated plasma insulin levels [67]. Rai et al. [93] showed that administering three units of insulin and 150, 200, and 250 mg/kg of *C. longa* dissolved in milk in STZ-induced diabetic rats lowered blood glucose levels. Sharma et al. [94] studied the antidiabetic efficacy of curcumin against STZ-induced toxicity in mice. A single dose of 65 mg/kg of STZ induced toxicity. Treatment of rats with 15 or 30 mg/kg of curcumin reduced plasma glucose levels, improved weight loss, decreased diabetic proteinuria, polyuria and elevated serum creatinine levels and blood urea nitrogen levels.

6.4. Anti-osteoarthritis activity

Nicoliche et al. [15] studied the anti-inflammatory efficacy of curcumin on zymosan-induced osteoarthritis in mice. Rats in treatment groups were administered 50 mg/kg of curcumin for 60 days. This study showed increased chondrocyte number and Col2 and SOX-5 expressions in curcumin treatment groups. *In vitro* tests carried out by Mathy-Hartert et al. [95] showed the inhibition of prostaglandin PGE_2, IL-6, IL-8, matrix metalloproteinase (MMP3) and NO synthesis in chondrocytes from human articular cartilage and human cartilage explants from osteoarthritic patients, upon treatment with 10–11 M of IL-1beta and 5–20 μM curcumin. Nonose et al. [18] investigated prednisone and curcumin to determine their anti-oxidative potency against zymosan-induced Arthritis in rats. Rats were treated with 1 and 8 mg/kg of prednisone and 100 mg/kg of curcumin. Curcumin increased the number of neutrophils and reduced joint inflammation during the first 6 h of administration; however, prednisone showed better anti-inflammatory potency over time. Curcumin has been shown to inhibit CFA-induced oedema in mice with 200 mg/kg turmeric [96]. These findings elucidate the anti-osteoarthritic efficacy of *C. longa* (Table 1).

6.5. Neuroprotective activity

Several studies have reported the neuroprotective effects of curcumin [97–99]. Reyes-Fermín et al. [97] examined curcumin's neuroprotective activity or α-mangostin in cerebellar granule neurons (CGNs). Neurons were treated with 18 μM of Iodoacetate. Treatment of neurons with curcumin and antioxidant α-mangostin resulted in the inhibition of ROS production and elevation of HO-1 expression. Yuliani et al. [98] reported the neuroprotective effect of the ethanolic extract of Turmeric on the brain antioxidant enzymes of mice injected with trimethylene. Results from this study showed the reduction of MDA levels and elevation of SOD, GSH, catalase and GPx enzyme activity. Xu et al. [19] examined the neuroprotective efficacy of curcumin against ischaemia-injured rats. The bioactive component reduced brain water, ameliorated nerve damage, decreased cerebral infarct volume and lessened abnormal cells (Table 1). Giacomeli et al. [100] reported the chemoprotective effect of curcumin-loaded lipid core nanocapsules in mice. Mice were treated with nanocapsules and 50 mg/kg of curcumin for 14 days. Findings from this study showed suppression of levels of mRNA expression of IL-6, NF-κB, TNF-α and IL-1β. *In vitro* analysis studied by Bollimpelli et al. [101] showed the neuroprotective potency of curcumin and nano curcumin on rotenone-induced neurotoxic SK-N-SH cells. Curcumin improved locomotor activity, recognition memory and spatial learning, lowering stress and anxiety levels in cadmium-induced toxic rats [75]. Ma and Guo [99] demonstrated the neuroprotective effect of *C. longa* extracts on SH-SY5Y cells. Salsolinol was used to induce toxicity in cells. Findings from this study showed that curcumin ameliorated cell growth inhibition and reduced ROS production (Table 1). Kadri et al. [102] reported *C. longa* neuroprotective efficacy against cerium chloride-induced toxicity.

6.6. Anti-inflammatory activity

In the study by Ukil et al. [103], curcumin exhibited anti-inflammatory activity by reducing produced NO and O_2^-in the colon of mice injected with TNBS at doses of 50, 100 or 300 mg/kg. Treatment of 3T3-L1 fibroblast cells with different concentrations of curcumin inhibited NF-κB activation and suppressed gene expression of TNF-α, IL-1β, IL-6, and COX-2 [104]. Soetikno et al. [105] examined the anti-inflammatory activity of curcumin against STZ-induced inflammation in mice. 100 mg/kg of curcumin was administered to mice three weeks after STZ injection. Administration of curcumin suppressed TNF-α, TGF-β1, ICAM-1, MCP-1, and IL-1β and also inhibited the activation of NF-κB. Treatment of rats with different doses of curcumin and curcumin nano-emulsions resulted in decreased TNF-α and IL-1β levels and attenuation of inflammatory cell infiltration [106]. Gupta et al. [107] reported the anti-inflammatory activity of aqueous *C. longa* and *Berberis aristata* extracts against anterior uveitis induced through i.p injection of lipopolysaccharide from *E. coli* in rabbits. Findings from this study showed decreased levels of TNF-α and inflammatory cell count. Kant et al. [108] demonstrated curcumin's ability to elevate the wound-healing property of Pluronic F-127 on STZ-induced toxic rats. Administration of combined doses resulted in an increased pace of wound contraction and healing. Kinney et al. [16] reported the inhibition of intestinal oedema formation and mastocytosis development in BALB/c mice upon administration of 300 μg of curcumin. These results reflect curcumin's ability to prevent allergies. The administration of 50 μM of curcumin on chondrocytes treated with 10 ng/mL IL-1β resulted in a decreased Matrix metalloproteinase-3 (MMP-3) [109]. Wang et al. [110] reported the downregulation of TNF-α and IL-6 expression in 3T3-L1 adipocytes upon treatment with 5, 10 and 20μmol/L of curcumin (Table 1).

6.7. Anti-obesity activity

Ejaz et al. [111] investigated the anti-obesity effect of curcumin on 3T3-L1 cell lines and C57BL/6 mice through *in vitro* and *in vivo* tests, respectively. Obesity in mice was induced by feeding rats with the AIN-93 diet; however, the administration of 500 mg/kg of curcumin suppressed body weight gain and also reduced VEGF mRNA and VEGFR-2 gene expression. *In vitro* study revealed the reduction of VEGFα expression and inhibition of angiogenesis in 3T3-L1 cells by curcumin. Results from both studies are consistent and elucidate the antidiabetic efficacy of curcumin (Table 1).

6.8. Anticancer activity

Levari et al. [112] reported the suppression of COX-2, EGFR expression and induction of apoptosis in several cell lines (PC-14, p34, H1299 and Panc-1 cell lines) treated with curcumin at doses between 0–50 μM. Jia et al. [17] investigated the antiproliferative effect of curcumin against MCF-7 and MDA-MB-231 cells. Results from this study showed that curcumin suppressed cell viability and proliferation. 50 μmol/L of curcumin inhibited phosphorylation and activation of NF-κB and IκBα and induced apoptosis in MDA-MB-435 cells emphasizing the need for more research on curcumin anticancer activity [113]. Akkoc et al. [114] investigated the chemoprotective efficacy of curcumin against MCF-7 cells. Findings from this study revealed a significant decrease in cell viability, induced autophagy, down-regulation of Bcl-2 and distortion of morphological arrangements. Curcumin induced

apoptosis and elevated levels of cleaved PARP at 50 μM, emphasizing its chemoprotective effect. Bachmeier et al. [115] reported the anticancer efficacy of curcumin against MDA-MB-231 cells. Treatment of cells with 25 μM of curcumin-induced apoptosis and reduced cell viability. Inoculation of curcumin on cells suppressed NFκB activation and inhibited the expression of MMP-1 and MMP-2 mRNA. Calaf et al. [116] investigated the anticancer activity of curcumin against MCF-10F cells. Curcumin inhibited cell growth and increased cell population in G_0/G_1 and G_2/M phases. Further analysis showed regulation of ADP, PARP-1 and H2AX (γ-H2AX). Xie et al. [117] showed the anticancer efficacy of curcumin against mice. Injury in mice was induced by surgery involving the occlusion of the right middle cerebral artery of mice. Mice were treated with 100, 200, 300, and 400 mg/kg of curcumin. Curcumin decreased the infarct volume induced due to surgery and inhibited morphological alterations. Western blot analysis and RT-PCR analysis showed that SAS, OC3, OECM-1, and NHOKs cells treated with different concentrations of curcumin increased IGFBP-5 mRNA expression and elevated C/EBPα binding to the IGFBP-5 promoter [118]. Divya and Pillai [119] reported curcumin's cytotoxic and antiproliferative efficacy against HeLa, SiHa, and C33A cells. The results from Dorai et al. [120] experiment utilizing curcumin treatment on mice injected with 1×10^6 of LNCaP cells showed the growth inhibitory effect of curcumin on cancer cells. These findings support *C. longa* chemopreventive and anticancer properties. Reddy and Aggarwal [78] reported the inhibition of kinase activity by curcumin in tumour cells. Gallardo and Calaf [121] reported the cytotoxic, antiproliferative efficacy of different doses of curcumin on MCF-10F, Tumor2 and MDA-MB-231 cells. RT-qPCR analysis revealed that curcumin decreased β-catenin, E-cadherin, and N-cadherin protein expression. Guo et al. [122] carried out *in vivo* test to determine the anticancer activity of the combined effect of curcumin and oxaliplatin. Experimental mice were injected with 1×10^6 LoVo cells. Findings from this study showed the accumulation of cells in the S and G2/M phases. Further analysis showed curcumin's ability to inhibit cell growth and induce apoptosis. Shao et al. [123] studied the cytotoxic potency of curcumin on MCF-7 and MDA-MB-231 cells, inhibiting VEGF, MMP-2 and b-FGF expression. Killian et al. [124] reported that treating PC-3 cells with a diet containing curcumin inhibited lung metastasis in mice. Jin et al. [125] demonstrated curcumin's upregulation of caspase-3 activity and miR-192–5p expression in NCL-H460, BEAS-2E and A549 cells. Results from this study showed that curcumin inhibited cell proliferation and inhibited PI3K/Akt signalling pathway in cells. In another study, Guan et al. [126] emphasized the anticancer potency of curcumin utilizing MDA-MB-231 cells in treatment. Curcumin decreased Akt expression, inhibited cell proliferation and migration and decreased the p62 protein level. Wong et al. [127] demonstrated the anticancer effect of curcumin and rapamycin. Treatment of SKN cells with these compounds co-administered increased cleaved PARP and caspase-3 activities (Table 1). Ushida et al. [128] carried out *in vivo* test to determine the anticancer potency of curcumin. A diet containing 500 ppm curcumin was administered to male F344 rats injected with 0.5 mg/kg of N-nitrosomethylbenzylamine (NMBA). Results showed reduced incidence and multiplicity of oesophagal neoplasms. Zhang et al. [129] elucidated curcumin anticancer activity with experiments inhibiting the growth of A549 cells upon curcumin treatment [130].

6.9. Anti-microbial activity

The antibacterial activities of curcumin against 65 clinical isolates of *H. pylori* were studied *in vivo* by De et al. [131]. Histological examinations revealed the complete eradication of *H. pylori* from the stomach of mice. In another study, Rai et al. [93] reported the significant antibacterial of curcumin against *Bacillus subtilis* 168, *Escherichia coli* BL21, and *E. coli* K12 MG1655. Curcumin inhibited the assembly of FtsZ protofilaments and inhibited bacterial growth and formation of Z rings. Also, curcumin showed antibacterial activity against *Staphylococcus aureus, B. subtilis, E. coli, Pseudomonas aeruginosa, and Vibrio cholerae,* with MIC values ranging from 125 to 1000 μg/mL [22]. Lobo de Sá et al. [132] demonstrated the anti-microbial activity of curcumin against *C. jejunii*. Kim et al. [133] assessed the anti-microbial activity of 200 and 500 mg/L of *C. longa* extract against HepG2 and HepG 2.2.15 cells. Curcumin and α-methyl cinnamaldehyde significantly inhibited the growth of 38 isolates of *Candida* strains. Kim et al. [134] tested the anti-microbial efficacy of different extracts (hexane, butanol, methanol, chloroform, ethyl acetate and water) of *C. longa* against *Pyricularia grisea, R. solani, Botrytis cinerea, P. infestans*. Also, different compounds (borneol, 1,8-cineole, sabinene, and turmerone) derived from *C. longa* were tested against phytopathogenic fungi. Curcumin showed the most fungicidal activity against tested bacteria. A separate *in vitro* study of the anti-microbial effect of ethyl acetate, methanol and water extract of *C. longa* on 13 clinical isolates of staphylococcal strains revealed MIC values (ethyl acetate extract 2 mg/mL), (methanol extract 8 mg/mL) and the (water extract MIC: 64 mg/mL) suggesting the good anti-oxidative property. Martins et al. [135] reported the inhibitory growth activity of curcumin on fungal and candida strains. Curcumin inhibited the adhesion of candida-tested species to human buccal epithelial cells (BEC). Kim et al. [136] demonstrated the curcumin and IFNα ability to suppress the replication of HCV in Huh7/Rep-Feo and Huh7 cells through the inhibition of Akt-SREBP-1 activation. *In vivo* study of *H. pylori*-infected mice administered with curcumin exhibited immense chemoprotective potential associated with eradicating *H. pylori cells* and healing mucosal damage [137].

Curcumin also showed anti-microbial activity with MIC values ranging from 125 to 250 μg/ml and a reduced *S. aureus* strain count [138]. This study showed the reduction of MIC values of antibiotics (oxacillin, ampicillin, ciprofloxacin, and norfloxacin) used in combined treatments. Tyagi et al. [139] reported the antibacterial activity of curcumin against *S. aureus, Enterococcus faecalis, E. coli and Pseudomonas aeruginosa* (Table 1)

6.10. Cardioprotective activity

Chung et al. [140] investigated the cardioprotective effect of curcumin utilizing cardiac fibroblasts isolated from rats. Fibroblasts were treated with 25 μM of curcumin and 10 ng/ml transforming growth factor (TGF)-β. Curcumin reduced cell migration and proliferation (Table 1).

6.11. Antidiarrheal activity

Sakai et al. [21] examined the antidiarrheal effect of curcumin against 50 mg/kg of 5-fluorouracil injected in mice. Rats in treatment groups were treated with 100 and 300 mg/kg of curcumin. RT-PCR analysis demonstrated the downregulation of the expression of CXCL1 and CXCL2 genes. Ouyang et al. [141] investigated the antidiarrheal activity of curcumin against Irinotecan (CPT-11) induced toxicity in BALB/c. Rats in treatment groups were treated with 100 mg/kg of curcumin. Findings from this study revealed the reduction in stool frequency and reversal of intestinal mucosa damage (Table 1).

7. Toxicological evaluation

Qureshi et al. [142] investigated extracts of *C. longa* to determine its toxicological effect in Swiss albino rats. The graded doses of 0.5, 1, and 3 g/kg of the plant extract were orally administered to rats in treatment groups. No toxicity was observed except at the maximum dosage (3 g/kg), which showed central nervous system stimulation. Intraperitoneal administration of 28 mg/kg of turmeric oil in rats daily for 14 days resulted in 20% mortality and a 36% increase at the end of the month [143]. Further analysis from this study showed that administering raw turmeric essential oil at 560 mg/kg for one month had neither toxicity nor mortality in rats. In another study, administration of 0.1,

0.25, and 0.5 g/kg of turmeric essential oil in rats did not produce toxicity and mortality [144]. Also, serum biomarkers (ALT, AST, ALP) analysed showed similar levels to rats in control groups [144].

Similarly, oral administration of curcumin at 5000 mg/kg in rats for 14 days did not show any toxic effect [145]. Polysaccharide extracts obtained from the rhizomes of *C. longa* were investigated to determine their toxicity. 5000 mg/kg of the extracts were administered, and necroscopic analysis did not show any pathological effects; the evaluation of body weight gain did not show any alteration [146]. Deshpande et al. [147] reported the hepatotoxic effect of Turmeric in rats. Administration of ethanolic turmeric extract altered liver weight and increased serum glutamic oxaloacetic transaminase activity. However, haemoglobin, kidneys, spleen, urea and creatinine remained unaffected. 2000 mg/kg of curcumin nanoparticles administered orally for 14 days in rats showed no toxicity in a study conducted by Dandekar et al. [148]. In a separate study, no abnormality or mortality was observed from the administration of 2000 mg/kg of solid lipid curcumin for 15 days, indicating its non-toxic nature [94]. The further necroscopic analysis did not exhibit any toxicity. Subchronic evaluation of 100 mg/kg *C. longa* administered in male and female rats for 90 days revealed an insignificant difference in mortality rate compared to rats in the control group. Furthermore, the haematological assessment showed reduced levels of red blood cells and white blood cells [142]. Aggarwal et al. [145] also reported the absence of toxicity and mortality upon administering 100, 500, and 1000 mg/kg curcuminoid essential oil in rats for 90 days.

8. Clinical trials on the therapeutic efficacy of *C. longa*

So far, some of the identified pharmacological activities of curcumin have been confirmed through clinical trials. In treating osteoarthritis and rheumatoid arthritis, oral administration of different doses of *C. longa* has been discovered to possess an anti-arthritic effect [150–154]. This therapeutic effect was observed in its significant effect on pain, joint swelling, reducing inflammatory markers, and improving disease activity score [150–152]. In patients confirmed to be suffering from type II diabetes mellitus, curcumin treatment improved endothelial function observed through a regulation of malondialdehyde (MDA), ET-1, IL-6 and TNF-α levels and ameliorating macroscopic proteinuria [155–156]. An oral or systemic application of *Curcuma longa* has been observed to improve several eye disorders, such as conjunctivitis, conjunctival xerosis and the degenerative conditions associated with cataracts [157,158]. In Alzheimer's patients, 12 months of oral administration of *Curcuma longa* led to increased Aβ40 deposits in the serum, which is an indication of the ability of curcumin to disaggregate Aβ-deposits-the significant cause of Alzheimer's disease [159]. A marked improvement in depression-related symptoms was also observed when patients were treated with oral doses of curcumin [160–163]. In children with recurrent respiratory tract infections, oral doses of curcumin supplementation improved immune modulation [164]. At doses of about 20–4000 mg, oral administration of curcumin led to an improvement in blood lipid profile parameters which is critical to the maintenance of cardiovascular health [165–167]. Curcumin, through its antioxidative properties, has also been observed to reduce erythrocyte malondialdehyde levels in patients diagnosed with tropical pancreatitis, and patients with Chronic Kidney Disease [168,169]. In a double blind, randomized control trial to determine the effects of curcumin on uraemic pruritus which is a symptom common in patients undergoing haemodialysis, a decrease in high sensitivity C-reactive protein was observed [170].

9. Conclusion and future perspectives

This study revealed that in-depth *in vivo* and *in vitro* studies had been conducted by various scientists to validate the ethnomedicinal uses of *C. longa* in the treatment, management and prevention of many diseases, including life-threatening illnesses like cancer and diabetes. Many researchers reported that *C. longa* contains numerous biologically active constituents with high antioxidant capacities. The health-promoting effect of *C. longa* can be attributed to the presence of biologically active compounds (phytochemicals and essential oils) and their rich-antioxidant properties. Furthermore, *C. longa* is used in culinary as a natural flavouring agent (spice) for the preparation of various foods across the globe due to its medicinal and distinctive organoleptic properties. In addition, experimental studies have confirmed several pharmacological activities of *C. longa,* such as; anticancer, anti-obesity, anti-oxidative, anti-osteoarthritis, hepatoprotective, antidiabetic, neuroprotective, anti-inflammatory, anti-obesity, anti-microbial, cardioprotective and antidiarrheal activity thus providing strong evidence that covers and supports its traditional uses for the treatment, prevention and management of various diseases. Based on the beneficial effects of *C. longa* and its biologically active compounds, it can be harnessed for developing pharmaceutical products and functional foods. However, there is a need for comprehensive studies in clinical trials and quality control to establish safe doses and efficacy of *C. longa* for treating various diseases. Also, further studies are required to ascertain the mechanism through which *C. longa* and its bioactive compounds offer protection against several diseases. This knowledge would aid their exploitation in the design and development of effective therapies for targeting diseases.

10. Limitations

This study has some limitations, which include; the inability to access few papers which were not open access and lack of sufficient literature to analyse few recognized properties. Also, due to the varying methodology used for the diverse articles, the data presented was not unified.

Author contributions

All authors listed have significantly contributed to the development and writing of this article. EJI, EAU and AHA: Conceptualization. EAU, EJI, AHA, MEU, EDD, LRE, TMD, AEO, BCO, and OED: Writing-orginal draft, Writing-review and editing.

Funding

The authors acknowledged the funding support received from Covenant University Centre for Research Innovation and Discovery (CUCRID).

Data availability statement

Not applicable.

Declaration of Competing Interest

The authors declare no conflict of interest.

Acknowledgements

Not applicable.

References

[1] S.C. Joshi, C.S. Mathela, Antioxidant and antibacterial activities of the leaf essential oil and its constituents furanodienone and curzerenone from Lindera pulcherrima (Nees.) Benth. ex hook. f, Pharmacogn. Res. 4 (2012) 80.
[2] B. Pant, Application of plant cell and tissue culture for the production of phytochemicals in medicinal plants, in: Infectious Diseases and Nanomedicine II, Springer, 2014, pp. 25–39.
[3] O.C. Ugbogu, O. Emmanuel, G.O. Agi, C. Ibe, C.N. Ekweogu, V.C. Ude, M.E. Uche, R.O. Nnanna, E.A. Ugbogu, A review on the traditional uses, phytochemistry, and pharmacological activities of clove basil (Ocimum gratissimum L.), Heliyon 7 (2021) e08404.
[4] V.O. Ikpeazu, E.A. Ugbogu, O. Emmanuel, C. Uche-Ikonne, B. Okoro, J. Nnaemeka, Evaluation of the safety of oral intake of aqueous extract of Stigma maydis (corn silk) in rats, Acta Sci. Pol. Technol. Aliment. 17 (2018) 387–397.

[5] S.N. Ijioma, O. Emmanuel, C.I. Nosiri, E.A. Ugbogu, Evaluation of toxicity profile and pharmacological potentials of Aju Mbaise polyherbal extract in rats, Sci. Afr. 11 (2021) e00681.
[6] M.P. Dimmito, A. Stefanucci, A. Della Valle, G. Scioli, A. Cichelli, A. Mollica, An overview on plants cannabinoids endorsed with cardiovascular effects, Biomed. Pharmacother. 142 (2021) 111963.
[7] K.I. Sinan, U. Akpulat, A.A. Aldahish, Y. Celik Altunoglu, M.C. Baloğlu, D. Zheleva-Dimitrova, R. Gevrenova, D. Lobine, M.F. Mahomoodally, O.K. Etienne, LC-MS/HRMS analysis, anti-cancer, anti-enzymatic and anti-oxidant effects of boerhavia diffusa extracts: a potential raw material for functional applications, Antioxidants 10 (2021) 2003.
[8] A. Sofowora, E. Ogunbodede, A. Onayade, The role and place of medicinal plants in the strategies for disease prevention, Afr. J. Tradit. Complement. Altern. Med. 10 (2013) 210–229.
[9] W.H. Organization, WHO Global Report On Traditional and Complementary Medicine 2019, World Health Organization, 2019.
[10] B.T. Tung, D.T. Nham, N.T. Hai, D.K. Thu, Curcuma longa, the polyphenolic curcumin compound and pharmacological effects on liver, Diet. Intervent. Liver Dis. (2019) 125–134.
[11] A.E.L.M. El-Kenawy, S.M.A. Hassan, A.M.M. Mohamed, H.M.A. Mohammed, Tumeric or Curcuma longa Linn, in: S.M. Nabavi, A.S. Silva (Eds.), Nonvitamin and Nonmineral Nutritional Supplements, Academic Press, 2019, pp. 447–453.
[12] B. Kocaadam, N. Şanlier, Curcumin, an active component of Turmeric (Curcuma longa), and its effects on health, Crit. Rev. Food Sci. Nutr. 57 (2017) 2889–2895.
[13] M. Uzunhisarcikli, A. Aslanturk, Hepatoprotective effects of curcumin and taurine against bisphenol A-induced liver injury in rats, Environ. Sci. Pollut. Res. 26 (2019) 37242–37253.
[14] H.-.Y. Lee, S.-.W. Kim, G.-.H. Lee, M.-.K. Choi, H.-.W. Chung, Y.-.C. Lee, H.-.R. Kim, H.J. Kwon, H.-.J. Chae, Curcumin and Curcuma longa L. extract ameliorate lipid accumulation through the regulation of the endoplasmic reticulum redox and ER stress, Sci. Reports 7 (2017) 1–14.
[15] T. Nicoliche, D.C. Maldonado, J. Faber, M.C.P.d. Silva, Evaluation of the articular cartilage in the knees of rats with induced Arthritis treated with curcumin, PLoS One 15 (2020) e0230228.
[16] S.R. Kinney, L. Carlson, J. Ser-Dolansky, C. Thompson, S. Shah, A. Gambrah, W. Xing, S.S. Schneider, C.B. Mathias, Curcumin ingestion inhibits mastocytosis and suppresses intestinal anaphylaxis in a murine model of food allergy, PLoS One 10 (2015) e0132467.
[17] T. Jia, L. Zhang, Y. Duan, M. Zhang, G. Wang, J. Zhang, Z. Zhao, The differential susceptibilities of MCF-7 and MDA-MB-231 cells to the cytotoxic effects of curcumin are associated with the PI3K/Akt-SKP2-Cip/Kips pathway, Cancer Cell Int. 14 (2014) 1–14.
[18] N. Nonose, J.A. Pereira, P.R.M. Machado, M.R. Rodrigues, D.T. Sato, C.A.R. Martinez, Oral administration of curcumin (Curcuma longa) can attenuate the neutrophil inflammatory response in zymosan-induced Arthritis in rats, Acta Cirurgica Bras. 29 (2014) 727–734.
[19] L. Xu, L. Ding, Y. Su, R. Shao, J. Liu, Y. Huang, Neuroprotective effects of curcumin against rats with focal cerebral ischemia-reperfusion injury, Int. J. Mol. Med. 43 (2019) 1879–1887.
[20] R. Essa, A.M. El Sadek, M.E. Baset, M.A. Rawash, D.G. Sami, M.T. Badawy, M.E. Mansour, H. Attia, M.K. Saadeldin, A. Abdellatif, Effects of Turmeric (Curcuma longa) Extract in streptozocin-induced diabetic model, J. Food Biochem. 43 (2019) e12988.
[21] H. Sakai, Y. Kai, A. Oguchi, M. Kimura, S. Tabata, M. Yaegashi, T. Saito, K. Sato, F. Sato, T. Yumoto, Curcumin Inhibits 5-Fluorouracil-induced Up-regulation of CXCL 1 and CXCL 2 of the colon associated with attenuation of diarrhoea development, Basic Clin. Pharmacol. Toxicol. 119 (2016) 540–547.
[22] N.K. Sasidharan, S.R. Sreekala, J. Jacob, B. Nambisan, *In vitro* synergistic effect of curcumin in combination with third generation cephalosporins against bacteria associated with infectious diarrhea, BioMed. Res. Int. 2014 (2014).
[23] B.B. Aggarwal, W. Yuan, S. Li, S.C. Gupta, Curcumin-free turmeric exhibits anti-inflammatory and anticancer activities: identification of novel components of Turmeric, Mol. Nutr. Food Res. 57 (2013) 1529–1542.
[24] T. Arablou, R. Kolahdouz-Mohammadi, Curcumin and endometriosis: review on potential roles and molecular mechanisms, Biomed. Pharmacother. 97 (2018) 91–97.
[25] A. Bhat, A.M. Mahalakshmi, B. Ray, S. Tuladhar, T.A. Hediyal, E. Manthiannem, J. Padamati, R. Chandra, S.B. Chidambaram, M.K. Sakharkar, Benefits of curcumin in brain disorders, Biofactors 45 (2019) 666–689.
[26] M. Dei Cas, R. Ghidoni, Dietary curcumin: correlation between bioavailability and health potential, Nutrients 11 (2019) 2147.
[27] A.R. Vaughn, A. Branum, R.K. Sivamani, Effects of Turmeric (Curcuma longa) on skin health: a systematic review of the clinical evidence, Phytother. Res. 30 (2016) 1243–1264.
[28] S. Fuloria, J. Mehta, A. Chandel, M. Sekar, N.N.I.M. Rani, M.Y. Begum, V. Subramaniyan, K. Chidambaram, L. Thangavelu, R. Nordin, A comprehensive review on the therapeutic potential of Curcuma longa Linn. in relation to its major active constituent curcumin, Front. Pharmacol. (2022) 13.
[29] B. Jyotirmayee, G. Mahalik, A review on selected pharmacological activities of Curcuma longa L, Int. J. Food Properties 25 (2022) 1377–1398.
[30] S. Prasad, B.B. Aggarwal, Turmeric, the golden spice, Herbal Medicine: Biomolecular and Clinical Aspects, 2nd edition, 2011.
[31] K. Karłowicz-Bodalska, S. Han, J. Freier, M. Smoleński, A. Bodalska, Curcuma longa as medicinal herb in the treatment of diabetic complications, Acta Pol. Pharm.–Drug Res. 74 (2017) 605–610.
[32] J. Jacob, Comparative studies in relation to the structure and biochemical properties of the active compounds in the volatile and nonvolatile fractions of Turmeric (C. longa) and ginger (Z. officinale), Stud. Nat. Products Chem 48 (2016) 101–135.
[33] H.P. Ammon, M.A. Wahl, Pharmacology of Curcuma longa, Planta Med. 57 (1991) 1–7.
[34] Z. Ayati, M. Ramezani, M.S. Amiri, A.T. Moghadam, H. Rahimi, A. Abdollahzade, A. Sahebkar, S.A. Emami, Ethnobotany, phytochemistry and traditional uses of Curcuma spp. and pharmacological profile of two important species (C. longa and C. zedoaria): a review, Curr. Pharm. Design 25 (2019) 871–935.
[35] G. Singh, I. Kapoor, P. Singh, C.S. de Heluani, M.P. de Lampasona, C.A. Catalan, Comparative study of chemical composition and antioxidant activity of fresh and dry rhizomes of Turmeric (Curcuma longa Linn, Food Chem. Toxicol. 48 (2010) 1026–1031.
[36] R. Abe, K. Ohtani, An ethnobotanical study of medicinal plants and traditional therapies on Batan Island, the Philippines, J. Ethnopharmacol. 145 (2013) 554–565.
[37] H.M. Ahmed, Ethnopharmacobotanical study on the medicinal plants used by herbalists in Sulaymaniyah Province, Kurdistan, Iraq, J. Ethnobiol. Ethnomed. 12 (2016) 1–17.
[38] H. Kim, M.-.J. Song, Analysis and recordings of orally transmitted knowledge about medicinal plants in the southern mountainous region of Korea, J. Ethnopharmacol. 134 (2011) 676–696.
[39] A. Merzouki, F. Ed-Derfoufi, J.M. Mesa, Contribution to the knowledge of Rifian traditional medicine. II: folk medicine in Ksar Lakbir district (NW Morocco), Fitoterapia 71 (2000) 278–307.
[40] C.A. Lans, Ethnomedicines used in Trinidad and Tobago for urinary problems and diabetes mellitus, J. Ethnobiol. Ethnomed. 2 (2006) 1–11.
[41] R. Bussmann, P.Z. NY, C. Romero, R.E. Hart, Astonishing diversity-the medicinal plant markets of Bogotá, Colombia, J. Ethnobiol. Ethnomed. (2018) 14.
[42] S.C. Gupta, S. Patchva, B.B. Aggarwal, Therapeutic roles of curcumin: lessons learned from clinical trials, AAPS J. 15 (2013) 195–218.
[43] L. Czernicka, A. Grzegorczyk, Z. Marzec, B. Antosiewicz, A. Malm, W. Kukula-Koch, Antimicrobial potential of single metabolites of Curcuma longa assessed in the total extract by thin-layer chromatography-based bioautography and image analysis, Int. J. Mol. Sci. 20 (2019) 898.
[44] T. Yuan, C. Zhang, C. Qiu, G. Xia, F. Wang, B. Lin, H. Li, L. Chen, Chemical constituents from Curcuma longa L. and their inhibitory effects of nitric oxide production, Nat. Product Res. 32 (2018) 1887–1892.
[45] E. Abdel-Lateef, F. Mahmoud, O. Hammam, E. El-Ahwany, E. El-Wakil, S. Kandil, H. Abu Taleb, M. El-Sayed, H. Hassenein, Bioactive chemical constituents of Curcuma longa L. rhizomes extract inhibit the growth of human hepatoma cell line (HepG2), Acta Pharm. 66 (2016) 387–398.
[46] S. Sabir, A. Zeb, M. Mahmood, S. Abbas, Z. Ahmad, N. Iqbal, Phytochemical analysis and biological activities of ethanolic extract of Curcuma longa rhizome, Brazilian J. Biol. 81 (2020) 737–740.
[47] T. Chumroenphat, I. Somboonwatthanakul, S. Saensouk, S. Siriamornpun, Changes in curcuminoids and chemical components of Turmeric (Curcuma longa L.) under freeze-drying and low-temperature drying methods, Food Chem. 339 (2021) 128121.
[48] L. Wang, M. Zhang, C. Zhang, Z. Wang, Alkaloid and sesquiterpenes from the root tuber of Curcuma longa, Acta Pharm. Sin. 43 (2008) 724–727.
[49] W. Li, S. Wang, J. Feng, Y. Xiao, X. Xue, H. Zhang, Y. Wang, X. Liang, Structure elucidation and NMR assignments for curcuminoids from the rhizomes of Curcuma longa, Magnetic Reson. Chem 47 (2009) 902–908.
[50] J. Akter, M.Z. Islam, K. Takara, M.A. Hossain, A. Sano, Isolation and structural elucidation of antifungal compounds from Ryudai gold (Curcuma longa) against Fusarium solani sensu lato isolated from American manatee, Comp. Biochem. Physiol. Part C: Toxicol. Pharmacol. 219 (2019) 87–94.
[51] M. D'Auria, R. Racioppi, Solid phase microextraction and gas chromatography mass spectrometry analysis of Zingiber officinale and Curcuma longa, Nat. Product Res 33 (2019) 2125–2127.
[52] J. Xu, F. Ji, J. Kang, H. Wang, S. Li, D.-.Q. Jin, Q. Zhang, H. Sun, Y. Guo, Absolute configurations and NO inhibitory activities of terpenoids from Curcuma longa, J. Agric. Food Chem. 63 (2015) 5805–5812.
[53] Y. Lu, J. Wang, G. Shen, J. Liu, H. Zhu, J. Zhao, S. He, Rapid Determination and quality control of pharmacological volatiles of turmeric (Curcuma longa L.) by fast gas chromatography–surface acoustic wave sensor, Molecules 26 (2021) 5797.
[54] H. Lee, Antiplatelet property of Curcuma longa L. rhizome-derived ar-turmerone, Biores. Technol. 97 (2006) 1372–1376.
[55] D. Jaiswal, S. Agrawal, Ultraviolet-B induced changes in physiology, phenylpropanoid pathway, and essential oil composition in two Curcuma species (C. caesia Roxb. and C. longa L.), Ecotoxicol. Environ. Safety 208 (2021) 111739.
[56] F.-.X. Xu, J.-.Y. Zhang, J. Jin, Z.-.G. Li, Y.-.B. She, M.-.R. Lee, Microwave-assisted natural deep eutectic solvents pretreatment followed by hydrodistillation coupled with GC-MS for analysis of essential oil from Turmeric (Curcuma longa L.), J. Oleo Sci. 70 (2021) 1481–1494.
[57] T.B. Le, C. Beaufay, D.T. Nghiem, T.A. Pham, M.-.P. Mingeot-Leclercq, J. Quetin-Leclercq, Evaluation of the anti-trypanosomal activity of vietnamese essential oils, with emphasis on Curcuma longa L. and its components, Molecules 24 (2019) 1158.
[58] Z. Chen, L. Quan, H. Zhou, Y. Zhao, P. Chen, L. Hu, Z. Yang, C. Hu, D. Cao, Screening of active fractions from Curcuma Longa Radix isolated by HPLC and GC-MS for promotion of blood circulation and relief of pain, J. Ethnopharmacol. 234 (2019) 68–75.
[59] F.D. Ferreira, S.A.G. Mossini, F.M.D. Ferreira, C.C. Arrotéia, C.L. da Costa, C.V. Nakamura, M. Machinski Junior, The inhibitory effects of Curcuma longa L. essential oil and curcumin on Aspergillus flavus link growth and morphology, Sci. World J. 2013 (2013).

[60] A. Kumar, K. Agarwal, M. Singh, A. Saxena, P. Yadav, A.K. Maurya, A. Yadav, S. Tandon, D. Chanda, D.U. Bawankule, Essential oil from waste leaves of Curcuma longa L. alleviates skin inflammation, Inflammopharmacology 26 (2018) 1245–1255.
[61] K.H. Lee, B.S. Kim, K.S. Keum, H.H. Yu, Y.H. Kim, B.S. Chang, J.Y. Ra, H.D. Moon, B.R. Seo, N.Y. Choi, Essential oil of Curcuma longa inhibits Streptococcus mutans biofilm formation, J. Food Sci. 76 (2011) H226–H230.
[62] L. Yarru, R. Settivari, N. Gowda, E. Antoniou, D. Ledoux, G. Rottinghaus, Effects of Turmeric (Curcuma longa) on the expression of hepatic genes associated with biotransformation, antioxidant, and immune systems in broiler chicks fed aflatoxin, Poult. Sci. 88 (2009) 2620–2627.
[63] Y. Sumanont, Y. Murakami, M. Tohda, O. Vajragupta, K. Matsumoto, H. Watanabe, Evaluation of the nitric oxide radical scavenging activity of manganese complexes of curcumin and its derivative, Biol. Pharm. Bull. 27 (2004) 170–173.
[64] N. Altıntoprak, M. Kar, M. Acar, M. Berkoz, N.B. Muluk, C. Cingi, Antioxidant activities of curcumin in allergic rhinitis, Eur. Arch. Oto-Rhino-Laryngol. 273 (2016) 3765–3773.
[65] S. Fujisawa, T. Atsumi, M. Ishihara, Y. Kadoma, Cytotoxicity, ROS-generation activity and radical-scavenging activity of curcumin and related compounds, Anticancer Res. 24 (2004) 563–570.
[66] H. Eshrat, M.A. Hussain, Hypoglycemic, hypolipidemic and antioxidant properties of combination of Curcumin fromCurcuma longa, Linn, and partially purified product fromAbroma augusta, Linn. in streptozotocin induced diabetes, Indian J. Clin. Biochem. 17 (2002) 33.
[67] P. Murugan, L. Pari, Antioxidant effect of tetrahydrocurcumin in streptozotocin–nicotinamide induced diabetic rats, Life Sci. 79 (2006) 1720–1728.
[68] P. Suryanarayana, A. Satyanarayana, N. Balakrishna, P.U. Kumar, G.B. Reddy, Effect of Turmeric and curcumin on oxidative stress and antioxidant enzymes in streptozotocin-induced diabetic rat, Med. Sci. Monitor 13 (2007) BR286–BR292.
[69] S. Samarghandian, M. Azimi-Nezhad, T. Farkhondeh, F. Samini, Anti-oxidative effects of curcumin on immobilization-induced oxidative stress in rat brain, liver and kidney, Biomed. Pharmacother. 87 (2017) 223–229.
[70] T. Ak, İ. Gülçin, Antioxidant and radical scavenging properties of curcumin, Chemico-Biol. Interact. 174 (2008) 27–37.
[71] A. Barzegar, A.A. Moosavi-Movahedi, Intracellular ROS protection efficiency and free radical-scavenging activity of curcumin, PLoS One 6 (2011) e26012.
[72] M. Rao, Nitric oxide scavenging by curcuminoids, J. Pharm. Pharmacol. 49 (1997) 105–107.
[73] S. Gao, X. Duan, X. Wang, D. Dong, D. Liu, X. Li, G. Sun, B. Li, Curcumin attenuates arsenic-induced hepatic injuries and oxidative stress in experimental mice through activation of Nrf2 pathway, promotion of arsenic methylation and urinary excretion, Food Chem. Toxicol. 59 (2013) 739–747.
[74] C. Girish, S. Pradhan, Hepatoprotective activities of picroliv, curcumin, and ellagic acid compared to silymarin on carbontetrachloride-induced liver toxicity in mice, J. Pharmacol. Pharmacother. 3 (2012) 149–155.
[75] D. Namgyal, S. Ali, R. Mehta, M. Sarwat, The neuroprotective effect of curcumin against Cd-induced neurotoxicity and hippocampal neurogenesis promotion through CREB-BDNF signaling pathway, Toxicology 442 (2020) 152542.
[76] J.-p. Liu, L. Feng, M.-m. Zhu, R.-.S. Wang, M.-h. Zhang, S.-y. Hu, X.-b. Jia, J.-.J. Wu, The *in vitro* protective effects of curcumin and demethoxycurcumin in Curcuma longa extract on advanced glycation end products-induced mesangial cell apoptosis and oxidative stress, Planta Med. 78 (2012) 1757–1760.
[77] R. Fernández-Marín, S.C. Fernandes, M.A. Andrés, J. Labidi, Microwave-assisted extraction of curcuma longa l. Oil: optimization, chemical structure and composition, antioxidant activity and comparison with conventional soxhlet extraction, Molecules 26 (2021) 1516.
[78] S. Reddy, B.B. Aggarwal, Curcumin is a non-competitive and selective inhibitor of phosphorylase kinase, FEBS Lett. 341 (1994) 19–22.
[79] S. Zhai, D. Ruan, Y. Zhu, M. Li, H. Ye, W. Wang, L. Yang, Protective effect of curcumin on ochratoxin A–induced liver oxidative injury in duck is mediated by modulating lipid metabolism and the intestinal microbiota, Poult. Sci. 99 (2020) 1124–1134.
[80] M. Sengupta, G.D. Sharma, B. Chakraborty, Hepatoprotective and immunomodulatory properties of aqueous extract of Curcuma longa in carbon tetra chloride intoxicated Swiss albino mice, Asian Pacific J. Trop. Biomed. 1 (2011) 193–199.
[81] D. Banji, J. Pinnapureddy, O.J. Banji, A. Saidulu, M.S. Hayath, Synergistic activity of curcumin with methotrexate in ameliorating Freund's Complete Adjuvant induced Arthritis with reduced hepatotoxicity in experimental animals, Euro. J. Pharmacol. 668 (2011) 293–298.
[82] R. Bruck, M. Ashkenazi, S. Weiss, I. Goldiner, H. Shapiro, H. Aeed, O. Genina, Z. Helpern, M. Pines, Prevention of liver cirrhosis in rats by curcumin, Liver Int. 27 (2007) 373–383.
[83] D. Joshi, D.K. Mittal, S. Shukla, S.K. Srivastav, V.A. Dixit, Curcuma longa Linn. extract and curcumin protect CYP 2E1 enzymatic activity against mercuric chloride-induced hepatotoxicity and oxidative stress: a protective approach, Exp. Toxicol. Pathol. 69 (2017) 373–382.
[84] E.O. Farombi, S. Shrotriya, H.-.K. Na, S.-.H. Kim, Y.-.J. Surh, Curcumin attenuates dimethylnitrosamine-induced liver injury in rats through Nrf2-mediated induction of heme oxygenase-1, Food Chem. Toxicol. 46 (2008) 1279–1287.
[85] S. Li, R. Liu, G. Wei, G. Guo, H. Yu, Y. Zhang, M. Ishfaq, S.A. Fazilani, X. Zhang, Curcumin protects against Aflatoxin B1-induced liver injury in broilers via the modulation of long non-coding RNA expression, Ecotoxicol. Environ. Saf. 208 (2021) 111725.
[86] V.O. Gutierres, C.M. Pinheiro, R.P. Assis, R.C. Vendramini, M.T. Pepato, I.L. Brunetti, Curcumin-supplemented yoghurt improves physiological and biochemical markers of experimental diabetes, British J. Nutr. 108 (2012) 440–448.
[87] K. Tikoo, R. Meena, D. Kabra, A. Gaikwad, Change in post-translational modifications of histone H3, heat-shock protein-27 and MAP kinase p38 expression by curcumin in streptozotocin-induced type I diabetic nephropathy, Br. J. Pharmacol. 153 (2008) 1225–1231.
[88] P.S. Babu, K. Srinivasan, Amelioration of renal lesions associated with diabetes by dietary curcumin in streptozotocin diabetic rats, Mol. Cell. Biochem. 181 (1998) 87–96.
[89] J. Chiu, Z.A. Khan, H. Farhangkhoee, S. Chakrabarti, Curcumin prevents diabetes-associated abnormalities in the kidneys by inhibiting p300 and nuclear factor-κB, Nutrition 25 (2009) 964–972.
[90] F. Yang, J. Yu, F. Ke, M. Lan, D. Li, K. Tan, J. Ling, Y. Wang, K. Wu, D. Li, Curcumin alleviates diabetic retinopathy in experimental diabetic rats, Ophthalmic Res. 60 (2018) 43–54.
[91] M.F. El-Azab, F.M. Attia, A.M. El-Mowafy, Novel role of curcumin combined with bone marrow transplantation in reversing experimental diabetes: effects on pancreatic islet regeneration, oxidative stress, and inflammatory cytokines, Euro. J. Pharmacol. 658 (2011) 41–48.
[92] M. Kuroda, Y. Mimaki, T. Nishiyama, T. Mae, H. Kishida, M. Tsukagawa, K. Takahashi, T. Kawada, K. Nakagawa, M. Kitahara, Hypoglycemic effects of Turmeric (Curcuma longa L. rhizomes) on genetically diabetic KK-Ay mice, Biol. Pharm. Bull. 28 (2005) 937–939.
[93] P. Rai, D. Jaiswal, S. Mehta, D. Rai, B. Sharma, G. Watal, Effect of Curcuma longa freeze dried rhizome powder with milk in STZ induced diabetic rats, Indian J. Clin. Biochem. 25 (2010) 175–181.
[94] S. Sharma, S.K. Kulkarni, K. Chopra, Curcumin, the active principle of Turmeric (Curcuma longa), ameliorates diabetic nephropathy in rats, Clin. Experi. Pharmacol. Physiol. 33 (2006) 940–945.
[95] M. Mathy-Hartert, I. Jacquemond-Collet, F. Priem, C. Sanchez, C. Lambert, Y. Henrotin, Curcumin inhibits pro-inflammatory mediators and metalloproteinase-3 production by chondrocytes, Inflam. Res. 58 (2009) 899–908.
[96] G. Ramadan, M.A. Al-Kahtani, W.M. El-Sayed, Anti-inflammatory and anti-oxidant properties of Curcuma longa (Turmeric) *versus* Zingiber officinale (ginger) rhizomes in rat adjuvant-induced Arthritis, Inflammation 34 (2011) 291–301.
[97] L.M. Reyes-Fermín, S. González-Reyes, N.G. Tarco-Álvarez, M. Hernández-Nava, M. Orozco-Ibarra, J. Pedraza-Chaverri, Neuroprotective effect of α-mangostin and curcumin against iodoacetate-induced cell death, Nutr. Neurosci. 15 (2012) 34–41.
[98] S. Yuliani, Mustofa, G Partadiredja, The neuroprotective effects of an ethanolic turmeric (Curcuma longa L.) extract against trimethyltin-induced oxidative stress in rats, Nutr. Neurosci. 22 (2019) 797–804.
[99] X.W. Ma, R.Y. Guo, Dose-dependent effect of Curcuma longa for the treatment of Parkinson's disease, Experi. Therapeutic Med. 13 (2017) 1799–1805.
[100] R. Giacomeli, J.C. Izoton, R.B. Dos Santos, S.P. Boeira, C.R. Jesse, S.E. Haas, Neuroprotective effects of curcumin lipid-core nanocapsules in a model Alzheimer's disease induced by β-amyloid 1-42 peptide in aged female mice, Brain Res. 1721 (2019) 146325.
[101] V.S. Bollimpelli, P. Kumar, S. Kumari, A.K. Kondapi, Neuroprotective effect of curcumin-loaded lactoferrin nano particles against rotenone induced neurotoxicity, Neurochem. Int. 95 (2016) 37–45.
[102] Y. Kadri, R. Nciri, N. Brahmi, S. Saidi, A.H. Harrath, S. Alwasel, W. Aldahmash, A. El Feki, M.S. Allagui, Protective effects of Curcuma longa against neurobehavioral and neurochemical damage caused by cerium chloride in mice, Environ. Sci. Pollut. Res. 25 (2018) 19555–19565.
[103] A. Ukil, S. Maity, S. Karmakar, N. Datta, J. Vedasiromoni, P.K. Das, Curcumin, the major component of food flavour turmeric, reduces mucosal injury in trinitrobenzene sulphonic acid-induced colitis, Br. J. Pharmacol. 139 (2003) 209–218.
[104] A.M. Gonzales, R.A. Orlando, Curcumin and resveratrol inhibit nuclear factor-kappaB-mediated cytokine expression in adipocytes, Nutr. Metabol. 5 (2008) 1–13.
[105] V. Soetikno, F.R. Sari, P.T. Veeraveedu, R.A. Thandavarayan, M. Harima, V. Sukumaran, A.P. Lakshmanan, K. Suzuki, H. Kawachi, K. Watanabe, Curcumin ameliorates macrophage infiltration by inhibiting NF-κB activation and proinflammatory cytokines in streptozotocin induced-diabetic nephropathy, Nutr. Metabol. 8 (2011) 1–11.
[106] Z. Zheng, Y. Sun, Z. Liu, M. Zhang, C. Li, H. Cai, The effect of curcumin and its nanoformulation on adjuvant-induced Arthritis in rats, Drug Design. Develop. Therapy 9 (2015) 4931.
[107] S.K. Gupta, R. Agarwal, S. Srivastava, P. Agarwal, S.S. Agrawal, R. Saxena, N. Galpalli, The anti-inflammatory effects of Curcuma longa and Berberis aristata in endotoxin-induced uveitis in rabbits, Invest. Ophthalmol. Visual Sci. 49 (2008) 4036–4040.
[108] V. Kant, A. Gopal, N.N. Pathak, P. Kumar, S.K. Tandan, D. Kumar, Antioxidant and anti-inflammatory potential of curcumin accelerated the cutaneous wound healing in streptozotocin-induced diabetic rats, Int. Immunopharmacol. 20 (2014) 322–330.
[109] G. Schulze-Tanzil, A. Mobasheri, J. Sendzik, T. John, M. Shakibaei, Effects of Curcumin (Diferuloylmethane) on Nuclear Factor κB Signaling in Interleukin-1β-Stimulated Chondrocytes, Annals New York Acad. Sci. 1030 (2004) 578–586.
[110] W. Shao-Ling, L. Ying, W. Ying, C. Yan-Feng, N. Li-Xin, L. Song-Tao, S. Chang-Hao, Curcumin, a potential inhibitor of up-regulation of TNF-alpha and IL-6 induced by palmitate in 3T3-L1 adipocytes through NF-kappaB and JNK pathway, Biomed. Environ. Sci. 22 (2009) 32–39.
[111] A. Ejaz, D. Wu, P. Kwan, M. Meydani, Curcumin inhibits adipogenesis in 3T3-L1 adipocytes and angiogenesis and obesity in C57/BL mice, J. Nutr. 139 (2009) 919–925.

[112] S. Lev-Ari, A. Starr, A. Vexler, V. Karaush, V. Loew, J. Greif, E. Fenig, D. Aderka, R. Ben-Yosef, Inhibition of pancreatic and lung adenocarcinoma cell survival by curcumin is associated with increased apoptosis, down-regulation of COX-2 and EGFR and inhibition of Erk1/2 activity, Anticancer Res. 26 (2006) 4423–4430.
[113] B.B. Aggarwal, S. Shishodia, Y. Takada, S. Banerjee, R.A. Newman, C.E. Bueso-Ramos, J.E. Price, Curcumin suppresses the paclitaxel-induced nuclear factor-κB pathway in breast cancer cells and inhibits lung metastasis of human breast cancer in nude mice, Clin. Cancer Res. 11 (2005) 7490–7498.
[114] Y. Akkoç, Ö. Berrak, E.D. Arısan, P. Obakan, A. Çoker-Gürkan, N. Palavan-Ünsal, Inhibition of PI3K signaling triggered apoptotic potential of curcumin which is hindered by Bcl-2 through activation of autophagy in MCF-7 cells, Biomed. Pharmacother. 71 (2015) 161–171.
[115] B. Bachmeier, A. Nerlich, C. Iancu, M. Cilli, E. Schleicher, R. Vené, R. Dell'Eva, M. Jochum, A. Albini, U. Pfeffer, The chemopreventive polyphenol Curcumin prevents hematogenous breast cancer metastases in immunodeficient mice, Cell. Physiol. Biochem. 19 (2007) 137–152.
[116] G.M. Calaf, C. Echiburú-Chau, G. Wen, A.S. Balajee, D. Roy, Effect of curcumin on irradiated and estrogen-transformed human breast cell lines, Int. J. Oncol. 40 (2012) 436–442.
[117] C.J. Xie, A.P. Gu, J. Cai, Y. Wu, R.C. Chen, Curcumin protects neural cells against ischemic injury in N2a cells and mouse brain with ischemic stroke, Brain Behav 8 (2018) e00921.
[118] K.W. Chang, P.S. Hung, I.Y. Lin, C.P. Hou, L.K. Chen, Y.M. Tsai, S.C. Lin, Curcumin upregulates insulin-like growth factor binding protein-5 (IGFBP-5) and C/EBPα during oral cancer suppression, Int. J. Cancer 127 (2010) 9–20.
[119] C.S. Divya, M.R. Pillai, Antitumor action of curcumin in human papillomavirus associated cells involves downregulation of viral oncogenes, prevention of NFkB and AP-1 translocation, and modulation of apoptosis, Mol. Carcinogen. 45 (2006) 320–332.
[120] T. Dorai, N. Gehani, A. Katz, Therapeutic potential of curcumin in human prostate cancer—I. Curcumin induces apoptosis in both androgen-dependent and androgen-independent prostate cancer cells, Prostate Cancer Prostatic Dis. 3 (2000) 84–93.
[121] M. Gallardo, G.M. Calaf, Curcumin inhibits invasive capabilities through epithelial mesenchymal transition in breast cancer cell lines, Int. J. Oncol. 49 (2016) 1019–1027.
[122] L.d. Guo, Y.q. Shen, X.h. Zhao, L.j. Guo, Z.j. Yu, D. Wang, L.m. Liu, J.z. Liu, Curcumin combined with oxaliplatin effectively suppress colorectal carcinoma *in vivo* through inducing apoptosis, Phytother. Res. 29 (2015) 357–365.
[123] Z.M. Shao, Z.Z. Shen, C.H. Liu, M.R. Sartippour, V.L. Go, D. Heber, M. Nguyen, Curcumin exerts multiple suppressive effects on human breast carcinoma cells, Int. J. Cancer 98 (2002) 234–240.
[124] P.H. Killian, E. Kronski, K.M. Michalik, O. Barbieri, S. Astigiano, C.P. Sommerhoff, U. Pfeffer, A.G. Nerlich, B.E. Bachmeier, Curcumin inhibits prostate cancer metastasis *in vivo* by targeting the inflammatory cytokines CXCL1 and-2, Carcinogenesis 33 (2012) 2507–2519.
[125] H. Jin, F. Qiao, Y. Wang, Y. Xu, Y. Shang, Curcumin inhibits cell proliferation and induces apoptosis of human non-small cell lung cancer cells through the upregulation of miR-192-5p and suppression of PI3K/Akt signaling pathway, Oncol. Rep. 34 (2015) 2782–2789.
[126] F. Guan, Y. Ding, Y. Zhang, Y. Zhou, M. Li, C. Wang, Curcumin suppresses proliferation and migration of MDA-MB-231 breast cancer cells through autophagy-dependent Akt degradation, PLoS One 11 (2016) e0146553.
[127] T.F. Wong, T. Takeda, B. Li, K. Tsuiji, M. Kitamura, A. Kondo, N. Yaegashi, Curcumin disrupts uterine leiomyosarcoma cells through AKT-mTOR pathway inhibition, Gynecol. Oncol. 122 (2011) 141–148.
[128] J. Ushida, S. Sugie, K. Kawabata, Q.V. Pham, T. Tanaka, K. Fujii, H. Takeuchi, Y. Ito, H. Mori, Chemopreventive effect of curcumin on N-nitrosomethylbenzylamine-induced esophageal carcinogenesis in rats, Japanese J. Cancer Res. 91 (2000) 893–898.
[129] J. Zhang, T. Zhang, X. Ti, J. Shi, C. Wu, X. Ren, H. Yin, Curcumin promotes apoptosis in A549/DDP multidrug-resistant human lung adenocarcinoma cells through an miRNA signaling pathway, Biochem. Biophysic. Res. Comm. 399 (2010) 1–6.
[130] N. Khan, S. Shreaz, R. Bhatia, S.I. Ahmad, S. Muralidhar, N. Manzoor, L.A. Khan, Anticandidal activity of curcumin and methyl cinnamaldehyde, Fitoterapia 83 (2012) 434–440.
[131] R. De, P. Kundu, S. Swarnakar, T. Ramamurthy, A. Chowdhury, G.B. Nair, A.K. Mukhopadhyay, Antimicrobial activity of curcumin against Helicobacter pylori isolates from India and during infections in mice, Antimicrob. Agents Chemother. 53 (2009) 1592–1597.
[132] F.D. Lobo de Sá, E. Butkevych, P.K. Nattramilarasu, A. Fromm, S. Mousavi, V. Moos, J.C. Golz, K. Stingl, S. Kittler, D. Seinige, Curcumin mitigates immune-induced epithelial barrier dysfunction by Campylobacter jejuni, Int. J. Mol. Sci. 20 (2019) 4830.
[133] H.J. Kim, H.S. Yoo, J.C. Kim, C.S. Park, M.S. Choi, M. Kim, H. Choi, J.S. Min, Y.S. Kim, S.W. Yoon, Antiviral effect of Curcuma longa Linn extract against hepatitis B virus replication, J. Ethnopharmacol. 124 (2009) 189–196.
[134] M.-.K. Kim, G.-.J. Choi, H.-.S. Lee, Fungicidal property of Curcuma longa L. rhizome-derived curcumin against phytopathogenic fungi in a greenhouse, J. Agric. Food Chem. 51 (2003) 1578–1581.
[135] C. Martins, D. Da Silva, A. Neres, T. Magalhaes, G. Watanabe, L. Modolo, A. Sabino, A. De Fátima, M. De Resende, Curcumin as a promising antifungal of clinical interest, J. Antimicrob. Chemother. 63 (2009) 337–339.
[136] K. Kim, K.H. Kim, H.Y. Kim, H.K. Cho, N. Sakamoto, J. Cheong, Curcumin inhibits hepatitis C virus replication via suppressing the Akt-SREBP-1 pathway, FEBS Lett. 584 (2010) 707–712.
[137] P. Kundu, R. De, I. Pal, A.K. Mukhopadhyay, D.R. Saha, S. Swarnakar, Curcumin alleviates matrix metalloproteinase-3 and-9 activities during eradication of Helicobacter pylori infection in cultured cells and mice, PLoS One 6 (2011) e16306.
[138] S.-.H. Mun, D.-.K. Joung, Y.-.S. Kim, O.-.H. Kang, S.-.B. Kim, Y.-.S. Seo, Y.-.C. Kim, D.-.S. Lee, D.-.W. Shin, K.-.T. Kweon, Synergistic antibacterial effect of curcumin against methicillin-resistant Staphylococcus aureus, Phytomedicine 20 (2013) 714–718.
[139] P. Tyagi, M. Singh, H. Kumari, A. Kumari, K. Mukhopadhyay, Bactericidal activity of curcumin I is associated with damaging of bacterial membrane, PLoS One 10 (2015) e0121313.
[140] C.-.C. Chung, Y.-.H. Kao, J.-.P. Liou, Y.-.J. Chen, Curcumin suppress cardiac fibroblasts activities by regulating proliferation, migration, and the extracellular matrix, Acta Cardiol. Sin. 30 (2014) 474.
[141] M. Ouyang, Z. Luo, W. Zhang, D. Zhu, Y. Lu, J. Wu, X. Yao, Protective effect of curcumin against irinotecan-induced intestinal mucosal injury via attenuation of NF-κB activation, oxidative stress and endoplasmic reticulum stress, Int. J. Oncol. 54 (2019) 1376–1386.
[142] S. Qureshi, A. Shah, A. Ageel, Toxicity studies on Alpinia galanga and Curcuma longa, Planta Med. 58 (1992) 124–127.
[143] J.L. Funk, J.B. Frye, J.N. Oyarzo, H. Zhang, B.N. Timmermann, Anti-arthritic effects and toxicity of the essential oils of Turmeric (Curcuma longa L.), J. Agric. Food chem. 58 (2010) 842–849.
[144] V.B. Liju, K. Jeena, R. Kuttan, Acute and subchronic toxicity as well as mutagenic evaluation of essential oil from Turmeric (Curcuma longa L), Food Chem. Toxicol. 53 (2013) 52–61.
[145] M.L. Aggarwal, K.M. Chacko, B.T. Kuruvilla, Systematic and comprehensive investigation of the toxicity of curcuminoid-essential oil complex: a bioavailable turmeric formulation, Mol. Med. Rep. 13 (2016) 592–604.
[146] C.C. Velusami, S.R. Boddapati, S. Hongasandra Srinivasa, E.J. Richard, J.A. Joseph, M. Balasubramanian, A. Agarwal, Safety evaluation of turmeric polysaccharide extract: assessment of mutagenicity and acute oral toxicity, BioMed Res. Int. (2013) 2013.
[147] S. Deshpande, V. Lalitha, A. Ingle, A. Raste, S. Gadre, G. Maru, Subchronic oral toxicity of Turmeric and ethanolic turmeric extract in female mice and rats, Toxicol. Letters 95 (1998) 183–193.
[148] P. Dandekar, R. Dhumal, R. Jain, D. Tiwari, G. Vanage, V. Patravale, Toxicological evaluation of pH-sensitive nanoparticles of curcumin: acute, sub-acute and genotoxicity studies, Food Chem. Toxicol. 48 (2010) 2073–2089.
[149] A. Hussain, Hypoglycemic, hypolipidemic and antioxidant properties of combination ofCurcumin fromCurcuma longa, Linn, and partially purified product fromAbroma augusta, Linn. in streptozotocin induced diabetes, Indian J. Clin. Biochem. 17 (2002) 33–43.
[150] S. Dcodhar, R. Sethi, R. Srimal, Preliminary study on antirheumatic activity of curcumin (diferuloyl methane), Indian J. Med. Res. (2013) 138.
[151] R. Kulkarni, P. Patki, V. Jog, S. Gandage, B. Patwardhan, Treatment of osteoarthritis with a herbomineral formulation: a double-blind, placebo-controlled, cross-over study, J. Ethnopharmacol. 33 (1991) 91–95.
[152] V. Kuptniratsaikul, P. Dajpratham, W. Taechaarpornkul, M. Buntragulpoontawee, P. Lukkanapichonchut, C. Chootip, J. Saengsuwan, K. Tantayakom, S. Laongpech, Efficacy and safety of Curcuma domestica extracts compared with ibuprofen in patients with knee osteoarthritis: a multicenter study, Clin Interv Aging 9 (2014) 451.
[153] B. Chandran, A. Goel, A randomized, pilot study to assess the efficacy and safety of curcumin in patients with active rheumatoid arthritis, Phytother. Res. 96 (2012) 1719–1725.
[154] P. Pinsornsak, S. Niempoog, The efficacy of Curcuma Longa L. extract as an adjuvant 670 therapy in primary knee osteoarthritis: a randomized control trial, J. Med. Assoc. Thai. 95 (2012) S51–S58.
[155] S. Chuengsamarn, S. Rattanamongkolgul, R. Luechapudiporn, C. Phisalaphong, S. Jirawatnotai, Curcumin extract for prevention of type 2 diabetes, Diabetes Care. (2012) DC_120116.
[156] A. Vanaie, S. Shahidi, B. Iraj, Z. Siadat, M. Kabirzade, F. Shakiba, M. Mohammadi, H. Parvizian, Curcumin as a major active component of turmeric attenuates proteinuria in patients with overt diabetic nephropathy, *J. Res. Med. Sci.* Off. J. Isfahan Univ. Med. Sci. (2019) 24.
[157] P. Allegri, A. Mastromarino, P. Neri, Management of chronic anterior uveitis relapses: efficacy of oral phospholipidic curcumin treatment. Long-term follow-up, Clin. Ophthalmol. 4 (2010) 1201.
[158] F. Mazzolani, S. Togni, Oral administration of a curcumin-phospholipid delivery system for the treatment of central serous chorioretinopathy: a 12-month follow-up study, Clinical Ophthalmol. (2013) 9.
[159] J. Ringman, S. Frautschy, E. Teng, A. Begum, J. Bardens, M. Beigi, K. Gylys, V. Badmaev, D. Heath, L. Apostolova, Oral curcumin for Alzheimer's disease: tolerability and efficacy in a 24-week randomized, double blind, placebo-controlled study, Alzheimer's Res. Ther. 4 (2012) 43.
[160] J. Yu, L. Pei, Y. Zhang, Z. Wen, J. Yang, Chronic supplementation of curcumin enhances the efficacy of antidepressants in major depressive disorder: a randomized, double-blind, placebo-controlled pilot study, J. Clin. Psychopharmacol. 35 (2015) 406–410.
[161] H. Esmaily, A. Sahebkar, M. Iranshahi, S. Ganjali, A. Mohammadi, G. Ferns, Ghayour-Mobarhan M. An investigation of the effects of curcumin on anxiety and depression in obese individuals: a randomized controlled trial, Chin J Integr Med (2015) 332–338.
[162] J. Bergman, C. Miodownik, Y. Bersudsky, S. Sokolik, P. Lerner, A. Kreinin, J. Polakiewicz, Curcumin as an add-on to antidepressive treatment: a randomized, dou-

ble-blind, placebo-controlled, pilot clinical study, Clin. Neuropharmacol. 36 (2013) 73–77.
[163] J. Sanmukhani, V. Satodia, J. Trivedi, T. Patel, D. Tiwari, B. Panchal, A. Goel, C. Tripathi, Efficacy and safety of curcumin in major depressive disorder: a randomized controlled trial, Phytother. Res. 28 (2014) 579–585.
[164] G. Zuccotti, D. Trabattoni, M. Morelli, S. Borgonovo, L. Schneider, M. Clerici, Immune modulation by lactoferrin and curcumin in children with recurrent respiratory infections, J. Biol. Regul. Homeost. Agents 29 (2009) 119–123.
[165] I. Alwi, T. Santoso, S. Suyono, B. Sutrisna, F. Suyatna, S. Kresno, S. Ernie, The effect of curcumin on lipid level in patients with acute coronary syndrome, Acta Med. Indones 40 (2008) 201–210.
[166] L. Baum, S. Cheung, V. Mok, L. Lam, V. Leung, E. Hui, C. Ng, M. Chow, P. Ho, S. Lam, Curcumin effects on blood lipid profile in a 6-month human study, Pharmacol. Res. 56 (2007) 509–514.
[167] R. DiSilvestro, E. Joseph, S. Zhao, J. Bomser, Diverse effects of a low dose supplement of lipidated curcumin in healthy middle aged people, Nutr J. 11 (2012) 783 79.
[168] S. Durgaprasad, C. Pai, J. Alvres, A pilot study of the antioxidant effect of curcumin in tropical pancreatitis, Indian J. Med. Res. 122 (2005) 315.
[169] A.S. Jiménez-Osorio, W. García-Niño, S. González-Reyes, A.E. Álvarez-Mejía, S. Guerra-León, J. Salazar-Segovia, I. Falcón, H.M. de Oca-Solano, M. Madero, J. Pedraza-Chaverri, The effect of dietary supplementation with curcumin on redox status and Nrf2 activation in patients with nondiabetic or diabetic proteinuric chronic kidney disease: a pilot study, J. Ren. Nutr. 26 (4) (2016) 237–244.
[170] M. Pakfetrat, F. Basiri, L. Malekmakan, J. Roozbeh, Effects of turmeric on uremic pruritus in end stage renal disease patients: a double-blind randomized clinical trial, J. Nephrol. 27 (2) (2014) 203–207.