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REVIEW
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Cinnamomum Species: Bridging Phytochemistry Knowledge, Pharmacological Properties and Toxicological Safety for Health Benefits

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The genus *Cinnamomum* includes a number of plant species largely used as food, food additives and spices for a long time. Different traditional healing systems have used these plants as herbal remedies to cure diverse ailments. The aim of this comprehensive and updated review is to summarize the biodiversity of the genus *Cinnamomum*, its bioactive compounds, the mechanisms that underlie the pharmacological activities and molecular targets and toxicological safety. All the data in this review have been collected from databases and recent scientific literature including Web of Science, PubMed, ScienceDirect etc. The results showed that the bioactive compounds of *Cinnamomum* species possess antimicrobial, antidiabetic, antioxidant, anti-inflammatory, anticancer and neuroprotective effects. The preclinical (*in vitro*/*in vivo*) studies provided the possible molecular mechanisms of these action. As a novelty, recent clinical studies and toxicological data described in this paper support and confirm the pharmacological importance of the genus *Cinnamomum*. In conclusion, the obtained results from preclinical studies and clinical trials, as well as reduced side effects provide insights

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into future research of new drugs based on extracts and bioactive compounds from *Cinnamomum* plants.

Keywords: Ciannamomum spp., phytochemistry, Pharmacology, mechanisms of action, clinical trials, Toxicological data

INTRODUCTION

The *Cinnamomum* plants have been studied for its phyto-constituents and pharmacological properties as well as traditional medicinal significance. *Cinnamomum verum*, known as the "true cinnamon tree" and "Ceylon cinnamon tree" is an evergreen small, tree that belongs to the Lauraceae family. Along with other cinnamon species, such as *Cinnamomum cassia*, *Cinnamomum verum* etc., the tree bark is used to obtain cinnamon (Ribeiro-Santos et al., 2017). The ancient botanical name of this tree – *Cinnamomum zeylanicum*- derives from Ceylon the old name for Sri Lanka (Ribeiro-Santos et al., 2017). *Cinnamomum cassia*, also called "Chinese cinnamon," is an evergreen tree, native to South China; Chinese cinnamon being produced mainly in the southern regions and is also widely grown in the other areas of the South and East Asia (Bedigian, 2005). People used cinnamon obtained from a variety of *Cinnamomum* plants as a spice from ancient times. It is mentioned in the texts written in Sanskrit and in the Bible, as well as in the works of Herodotus and Pliny (Lu et al., 2011). In Egypt, *Cinnamomum zeylanicum* was used in the embalming process. It was also added to foods for preservation. Both in India and Europe, *Cinnamomum* species have been traditionally used in the treatment of respiratory viruses, especially combined with ginger (*Zingiber officinale*). Ginger stimulates blood circulation in the extremities (toes, fingers), and *Cinnamomum* plants are an alternative natural medicine for reducing muscle pain and other signs and symptoms of colds and flu. Other traditional uses include urinary tract infections, relieve the abdominal discomfort, and improves digestion, antidiabetic, analgesic, and neuroprotective effects (Ravindran et al., 2003).

All types of cinnamon contain the active ingredient cinnamaldehyde, which accounts for between 65 and 80% of the essential natural oil. Cinnamon is used in case of dyspepsia, flatulence, nausea, intestinal colic, slow digestion, diarrhea, and digestive atony. This antispastic effect is attributed to the natural chemical compound catechin that contributes to the reduction of nausea and vomiting. Also, its volatile oil can help better food processing by breaking down fat during digestion. The studies showed that cinnamon helps diabetic patients to metabolize sugar more easily. In the case of people with type II diabetes, the pancreas produces insulin, but their body cannot use it effectively for decreasing blood sugar concentration (Chen et al., 2012). The researchers have found in recent studies that cinnamon improves insulin's ability to metabolize glucose, helping to control blood sugar levels. It contains the antioxidant glutathione and a type of flavonoid called methyl hydroxychalcone polymer (MHCP) (Qin et al., 2010). The potential antidiabetic mechanism of cinnamon is associated with increasing the receptivity of adipose cells to the hormone insulin that regulates the metabolism of glucose and controls the level of sugar in the blood.

Cinnamon helps reduce pain due to its action of inhibiting prostaglandin. Cinnamaldehyde acts against the coagulation of platelets in the blood, which can hinder blood flow. It inhibits arachidonic acid's release (a trigger for the inflammatory response) from cell membranes (Vallianou et al., 2019). Therefore, cinnamon is useful for the pharmacotherapy of inflammatory diseases, such as rheumatoid arthritis (Rogoveanu et al., 2018; Shishehbor et al., 2018). Recent studies showed that the scent and aroma of cinnamon act as cognitive stimuli, which could improve memory, visual-motor capacity and virtual memory (Nussbaum et al., 2017), due to its compound cinnamic aldehyde. Experimental researches on rodents receiving cinnamic aldehyde have reported improvements in stress-induced depressive behaviors. Cinnamic aldehyde is administered orally in the treatment of behavioral and mental disorders. Recent findings in this regard may also be helpful in treating depression (Panickar et al., 2009).

Starting from the ethnopharmacological premises of the therapeutic beneficial effects of Cinnamomum genus, in this manuscript were highlighted, based on scientific evidence the potential current pharmacological mechanisms and human clinical studies for the benefits of human health. Therefore, this current work reviews the comprehensive and current knowledge on the phyto-constituents, potential mechanisms of the main pharmacological activities evidenced by preclinical studies (*in vivo, in vitro*), recent clinical trials and toxicological data regarding safety of *Cinnamomum* plants.

REVIEW METHODOLOGY

Scientific search engines Medline, PubMed, ScienceDirect and Scopus were searched to retrieve literature and cross-references using key words: "*Cinnamomum*," "phytochemistry," "pharmacology"; "mechanisms of action"; "toxicology." We included literature in relation to the bioactive compounds, pharmacological activities and underlying mechanism of action, clinical studies, toxicological and safety considerations of different *Cinnamomum* species. Plants' taxonomy was validated using The Plant List (http://www.theplantlist.org/), and chemical formulas were validated by consulting the PubChem chemical base data (http://pubchem.ncbi.nlm.nih.gov/search/#collection=compounds). Inclusion criteria: *in vitro*/*in vivo* pharmacological studies using cell lines and laboratory animals, studies involving extracts of the genus Cinnamomum, studies with obvious mechanisms of action. Exclusion criteria: studies that included homeopathic

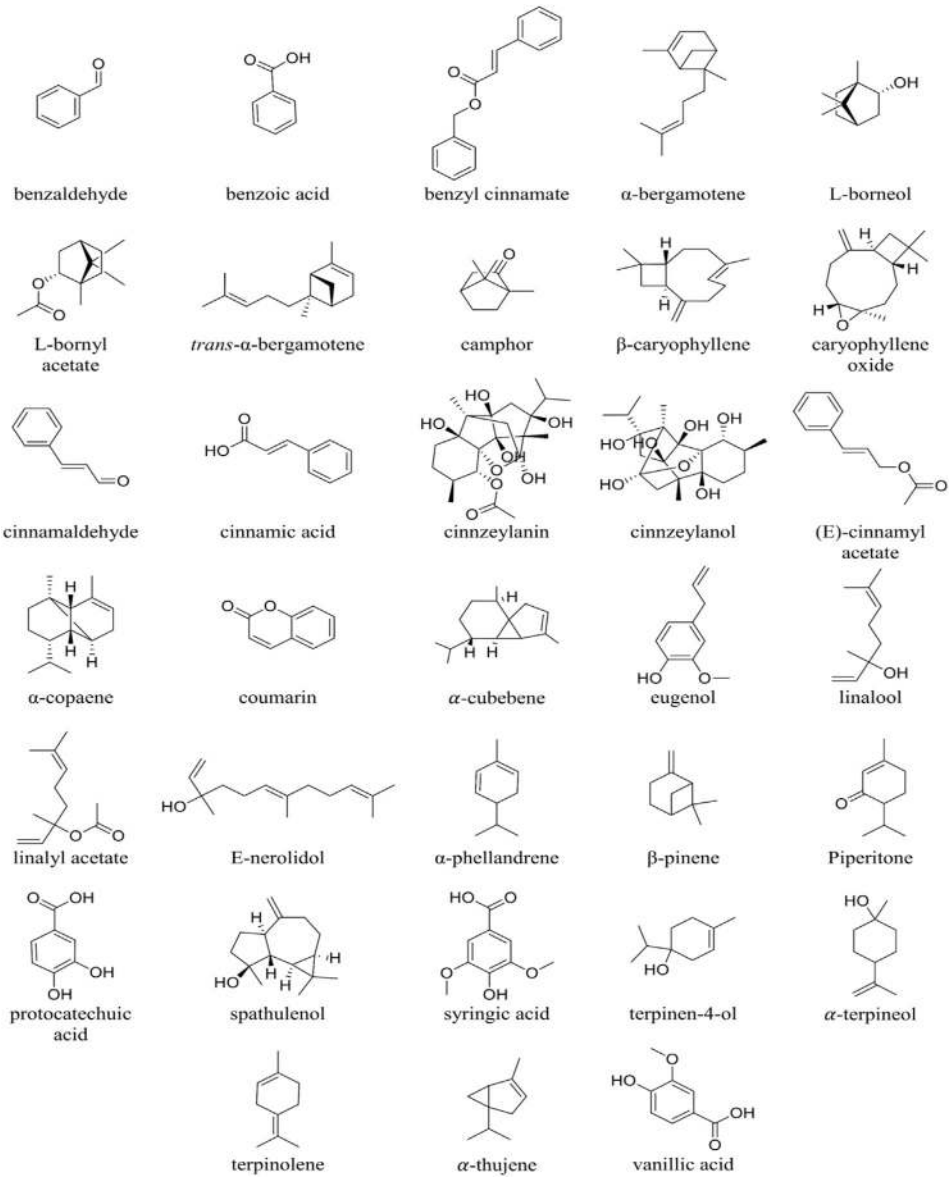

FIGURE 1 | Chemical structures of the phyto-constituents of *Cinnamomum* species.

preparations and other associated nutritional supplements, studies without explaining the mechanism of action.

PHYTOCHEMISTRY OF *CINNAMOMUM* GENUS

Chemical Composition

The chemical composition of cinnamon EOs (essential oils) varies depending on several factors that include the part of the plant used, growing season, age of trees, location, and extraction methods (Kaul et al., 2003; Barceloux, 2009; Wang et al., 2009; Chakraborty et al., 2015). Cinnamaldehyde and its analogs, butanolides, diterpenoids, lignans and several other compounds, are present in this genus. From the genus *Cinnamomum,* a total of 127 chemical compounds have been identified (Zhao and Ma, 2016).

Cinnamon presents a diversity of resinous compounds, including cinnamaldehyde, cinnamates, cinnamic acid and natural EOs (Senanayake et al., 1978) (**Figure 1**; **Table 1**). Over time, cinnamaldehyde changes color, absorbs oxygen and thus explains the appearance of the perfume and spicy taste (Singh et al., 2007). EOs contain a great variety of volatile natural compounds, such as *trans*-cinnamaldehyde, eugenol, cinnamyl acetate, L-borneol, *ß*-caryophyllene, caryophyllene oxide, L-bornyl acetate, *a*-thujene, *a*-terpineol, *a*-cubebene, terpinolene and E-nerolidol (Jantan and Goh, 1992; Jantan et al., 2003; Jantan et al., 2005; Chua et al., 2008; Abdelwahab

TABLE 1 | The most representative chemical compounds of *Cinnamomum* plants.

Plant parts	Compounds	Ref
Bark	cinnamaldehyde 65–80% eugenol 5–10%	Yanakiev. (2020)
Bark of root	camphor 58%	Rao and Gan. (2014)
Leaf	eugenol 70–90%, cinnamaldehyde 1–8%	Utchariyakiat et al. (2016)
Fruits	*trans*-cinnamyl acetate 40–50% caryophyllene 10–15%	Bakar et al. (2020)
Buds	α-bergamotene 27% terpene hydrocarbons 80% α-copaene 20%, terpenoids 10%	Barceloux. (2009)
Flowers	*trans*-cinnamyl acetate 40% *trans*-α-bergamotene 10% caryophylleneoxide 8%	Bakar et al. (2020)

et al., 2010; Tung et al., 2010; Geng et al., 2011). Spathulenol was reported as the major compound in leaf oil of *Cinnamomum altissimum* Kosterm (Jantan et al., 2003).

According to (Wang et al., 2009), eugenol (80%) is the main volatile compound in the EO of *Cinnamomum verum* J. Presl (synonym: *Cinnamomum zeylanicum* Blume) instead of *trans*-cinnamaldehyde (16.25%) and the other constituents such as: alcohols, aldehydes, ketones, alkanes, sulfides, and ethers. The chemical composition in the bark and leaf EOs of *C. verum* consists of high levels of eugenol (90.2%) and cinnamaldehyde (44.2%). The chemical constituents of *C. verum* bark EO include three major compounds and six minor chemical derivatives (Yang et al., 2012). Cinnamaldehyde (59%), benzaldehyde (12%) and eugenol (5%) are the major compounds, while the six minor constituents are α-phellandrene (1.1%), linalool (1.1%), benzoic acid (0.8%), β-caryophyllene (0.7%), linalyl acetate (0.6%) and benzyl cinnamate (0.6%). The most important compounds identified in the leaf oil of *C. verum* grown are eugenol (75%), linalool (8%) and piperitone (2.5%) (Raina et al., 2001).

Chemical constituents in the leaf EO of *Cinnamomum burmanni* (Nees & T. Nees) Blume are *trans*-cinnamaldehyde (60%), eugenol (18%) and coumarin (14%). Other constituents identified in the oils are alcohols, aldehydes, and ketones. The major components in the stem bark oil of *Cinnamomum iners* (Reinw. ex Nees & T. Nees) Blume are 1,8-cineole (41%), α-terpineol (15%) and terpinen-4-ol (14%). The other components identified are β-pinene (4.75%), γ-terpinolene (1.61%) and caryophyllene oxide (4.37%) (Wang et al., 2009).

Other minor constituents reported in cinnamon EO include: cinnamic acid, phenolic acids, oligopolymeric procyanidins, pentacyclic diterpenes, cinnzeylanol, and its acetyl derivative cinnzeylanine, mannitol, xylose, arabinose, xylanose, glucose, mucilage polysaccharides (European Scientific Cooperative on Phytotherapy, 2003). Several nonvolatile compounds have been found in cinnamon EOs such as cinncassiols, cinnzeylanol, cinnzeylanin, anhydrocinnzeylanol, anhydrocinnzeylanin, several benzyl isoquinoline alkaloids, cinnamic acid, β-sitosterol, flavanol glucosides, coumarin, protocatechuic acid, vanillic acid and syringic acid (Leela, 2008).

Cinnamomum's Natural Compounds: Pharmacokinetics, Bioavailability, Bioactivity and Metabolism

Considering the pharmacokinetics, bioavailability and metabolism of Cinnamomum active ingredients, very little works have been performed. Many studies described the role of bioactive compounds from the plants in enhancing bioavailability of some standard drugs (Salehi et al., 2020b).

Pharmacokinetics of cinnamic acid (CA) indicated the CA was readily absorbed and then metabolized quickly into hippuric acid (HA) when a decoction of *Ramulus Cinnamomi* (RC) [containing CA 7.62×10^{-5} mol/kg and cinnamaldehyde (CNMA) 1.77×10^{-5} mol/kg] was administered in rats via oral route. CNMA was found to be metabolized partially in stomach and small intestine into CA and almost fully metabolized in liver into CA before being absorbed into rat blood. The results indicated that plasma CA in RC group probably came from CNMA transformation in RC (Chen et al., 2009). Cinnamon also increased pioglitazone bioavailability via CYP3A4 enzyme inhibition in rat following oral administration owing to its possible use in combination with pioglitazone against diabetes (Mamindla et al., 2017). CA significantly inhibited rosuvastatin (RSV) (a specific breast cancer resistance protein) transport into rat bile thus enhanced the plasma exposure of the same (Basu et al., 2013).

In a recent study, comparative pharmacokinetic analysis of *Cinnamomum cassia* twigs' standard decoction and dispensing granules containing three phenolics such as cinnamic acid, vanillic acid and protocatechuic acid in rats revealed the AUC_{0-t} values of the compounds by LC–MS/MS (Tao et al., 2019).

PRECLINICAL STUDIES RELATED TO PHARMACOLOGICAL ACTIVITIES AND POTENTIAL MECHANISMS OF *CINNAMOMUM*'S PHYTO-CONSTITUENTS

Various traditional uses of *Cinnamomum* plants motivated a series of experimental investigations of the plant's pharmacological properties (Wang et al., 2020). Those experimental approaches tempted to validate the potential uses of these plants as therapeutic remedies. Studies have been reported on extracts and isolated compounds of *Cinnamomum* plants, investigating antibacterial, anti-diabetes, anti-inflammatory, antioxidant, antitumor, and neuroprotective properties.

Antibacterial Activity

In order to inhibit the growth and proliferation of pathogenic microorganisms, synthetic drugs have been commonly used for

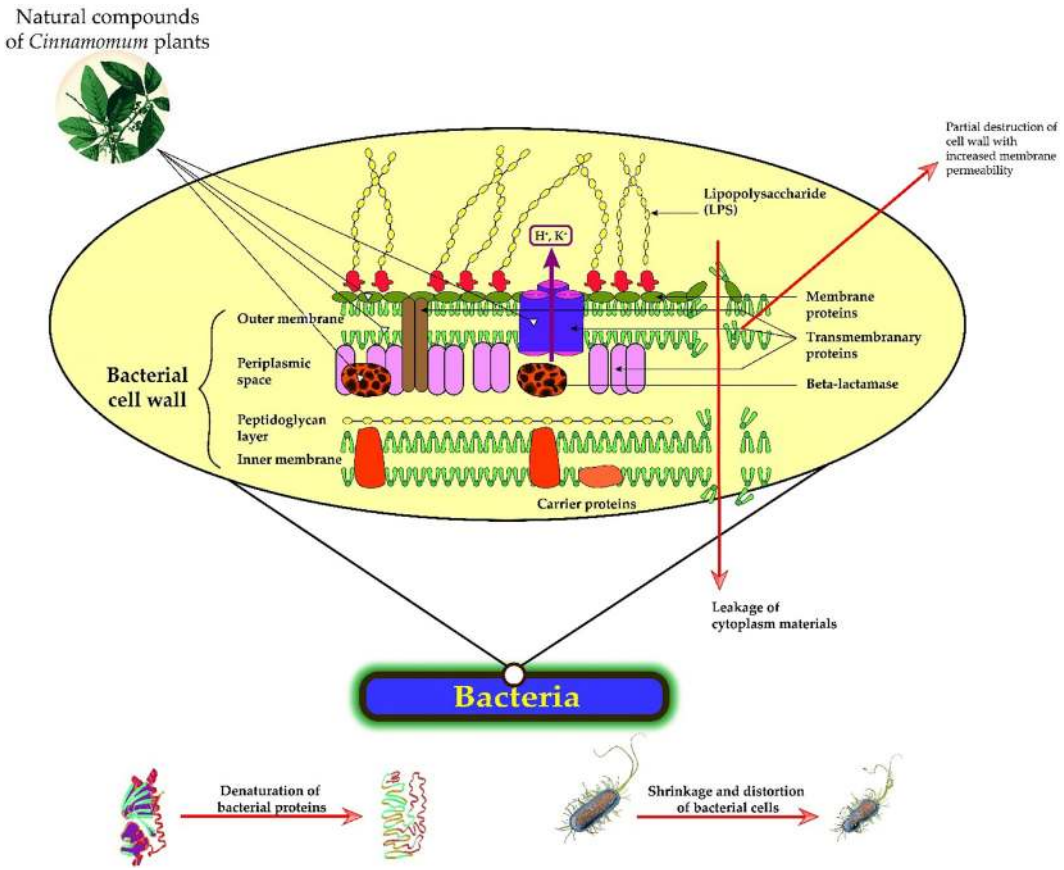

FIGURE 2 | Antibacterial properties of *Cinnamomum* plants' derivatives. The main potential mechanisms of antibacterial action are related to: 1) the partial degradation of the bacterial cell wall, 2) the increase of membrane permeability, 3) the leakage of cytoplasm materials, 4) the shrinkage of bacterial cells and prominent distortion, and 5) the alteration of secondary, tertiary structures and bacterial protein.

the treatment of microbial infections. The overuse of conventional antibacterial drugs could lead to serious side effects, including the selection of resistant bacterial strains and the development of antibiotic resistance during treatment, posing a real threat to global public health (Russell, 2002; Goyal et al., 2008; Călina et al., 2017; Ungureanu et al., 2017; Zlatian et al., 2018). Therefore, it is necessary to discover new sources of antibiotics such us natural antimicrobial compounds that could be an effective and cheaper alternative (Mbwambo et al., 2007; Salehi et al., 2019a).

The mechanisms underlying the antibacterial effects of natural derivatives of *Cinnamomum* plants are complex. Cinnamaldehyde, as well as eugenol, inhibited β-lactamase's production by the bacterium and destroyed its cell wall (Helander et al., 1998; Di Pasqua et al., 2007). Phenolic compounds such as carvacrol can also cause destruction of the cell cytoplasmic membrane (Ultee et al., 1999), and terpenes interact with the bacterial membrane by modifying its permeability (Lambert et al., 2001) and increasing the penetration of antibacterial agents. Essential oils of *Cinnamomum* contain a wide range of different groups of chemical compounds, suggesting that their antibacterial activity might have several mechanisms (Skandamis and Nychas, 2001; Carson et al., 2002). (**Figure 2**).

A recent study highlighted that MBC (minimum bactericidal concentration) and MIC (minimum inhibitory concentration) of the methanol extract of *C. burmanni* leaves were 625 and 2,500 μg/ml, against *Bacillus cereus*. For other bacterial strains (*Staphilococcus aureus*, *Listeria monocytogenes, Escherichia coli,* and *Salmonella anatum*), the values are >2,500 μg/ml for both concentrations (Shan et al., 2007).

The methanol extract of *Cinnamomum tamala* (Buch.-Ham.) T. Nees & Eberm. stem bark revealed MIC values of 256, 4,096, 4,096, and 2048 μg/ml against *Staphilococcus aureus*, *Streptococcus pyogenes*, *B. cereus* and *Bacillus subtilis*, respectively, with inhibition diameters ranging from 14.0 to 20.8 mm (Goyal et al., 2009). The aqueous extract of *C. verum* bark demonstrated antibacterial activity against *Moraxella cattarhalis* with MIC and MBC values of 120 and 240 mg/ml, respectively, and an inhibition zone of 11 mm (Rasheed and Thajuddin, 2011). (**Table 2**).

Regarding the EO of *C. osmophloeum* leaves, the MIC values were 200 and 500 μg/ml for the 9 bacteria tested (Chang et al., 2001), and the chemical components of this oil were similar to

those of *Cinnamomum cassia* (L.) J. Presl (Hu et al., 1985). In addition, (Oussalah et al., 2006) evaluated the antibacterial efficacy of essential oils of two *Cinnamomum* species: *C. cassi* and *C. verum* against *Pseudomonas putida* and found MIC values of 0.05 and 0.1 % wt/vol, respectively. In another study, the MIC values for the EO of *C. cassia* leaves were 500 ppm for *E. coli*, *B. cereus*, *Lactobacillus sakei* and 750 mg/ml for *Salmonella typhimurium* (Turgis et al., 2012).

The antibacterial potency of the methanol extract of *C. cassia* was also tested against different species of *E. coli* by the disk diffusion method and the microdilution (Kim et al., 2004). The *C. cassia* bark EO was tested on *L. monocytogenes* and *EPEC* with a zone of inhibition of 22.42 and 13.72 mm, respectively, and a MIC of 0.03 and 0.06 µg/ml respectively (de Oliveira et al., 2012). Another study on the same part of *C. cassia* investigated the permeability of the bacterial membrane by measuring the relative electrical conductivity, which increased with the increased concentration of the EO (Huang et al., 2014).

The antimicrobial property of *C. verum* EO was assayed against 21 bacteria strains, using MIC methods and disc diffusion. The EO highlighted the significant antibacterial activity against the tested strains. It showed higher activity against Gram-positive (*Enterococcus*, *Streptococcus*, *Staphylococcus*) and Gram-negative (*Pseudomonas aeruginosa*) bacteria strains. These results are consistent with those of Chao et al. (2000) revealing that bark oil of cinnamon completely inhibited the growth of selected Gram-negative and Gram-positive bacteria.

In vitro antibacterial efficacy of different EOs (Al-Bayati and Mohammed, 2009; Noudeh et al., 2010; Guerra et al., 2012; Utchariyakiat et al., 2016) and methanol extracts (Hameed et al., 2016) of *C. verum* bark was evaluated against Gram-positive and Gram-negative bacteria using broth dilution and diffusion methods. The obtained results showed that *C. verum* was able to inhibit all of the tested strains. Furthermore, the main chemical constituents of *C. cassia* and *C. verum* natural oils were eugenol cinnamaldehyde (Ross, 1976; Hu et al., 1985) which could inhibit microbial growth (Lee and Ahn, 1998; Ooi et al., 2006).

EOs of *Cinnamomum micranthum* f. kanehirae (Hayata) S. S. Ying (leaves and twigs) were effective against *Vibrio parahemolyticus*, *V. alginolyticus*, *V. vulnificus*, *Lactococcus garvieae*, *Debaryomyces hansenii*, *Photobacteria damsel*, *Streptococcus* sp. and *Aeromonas hydrophila*, with diameters reduction from 0.1 to 1 cm (Yeh et al., 2009). The observed difference may be due to the difference of antibacterial constituents in leaves and twigs. The antibacterial screening of EO samples extracted from *Cinnamomum bejolghota* (Buch.-Ham). Sweet was evaluated using disc diffusion assay against zoonotic enteropathogens and showed promising antibacterial activity (Wannissorn et al., 2005). Indeed, EOs are complexes of antibacterial agents including natural aromatic and volatile compounds (Loy et al., 2001).

The volatile oils and extracts from the stem bark of *Cinnamomum impressicostatum* Kosterm., *C. altissimum* and *C. porrectum* (Roxb.) Kosterm showed high antibacterial activity against Gram-positive and Gram-negative bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA). Some tested extracts exhibited relevant activity against MRSA compared with methicillin-sensitive *S. aureus* (MSSA). The highest inhibition zone (21.0 mm) was measured for *C. impressicostatum* stem-bark water extract against MRSA with MIC and MBC values of 19.5 and 39.0 µg/ml, respectively (Buru et al., 2014). The leaf oil of *Cinnamomum chemungianum* M. Mohanan and A. N. Henry enhanced a moderate activity against the tested bacteria (Rameshkumar et al., 2007).

Agarwal et al. (2019) used *C. tamala* leaf extract to synthesize eco-friendly zinc oxide nanoparticles with important antibacterial effects against *S. aureus*. Authors showed that these nanoparticles induced reduction in bacterial growth, in a time and concentration-dependent pattern, due to membrane damage that leads to leakage of intracellular proteins and cellular contents. On the other hand, *C. verum* EOs exhibited remarkable inhibitory effects of *Staphylococcus aureus* multi-drug resistant (MDR). Indeed, cinnamon oil at concentrations of 3.12% strongly inhibited all the *Streptococcus mutans* isolated with the MIC values of 12.8–51.2 and 64–256 mg/ml, respectively (Fani and Kohanteb, 2011). (Rossi et al., 2019) showed that *C. verum* EOs inhibited the adhesion of *Salmonella enterica* which involved the reduction of polyphenol oxidase activity. (Wu et al., 2019) showed that *C. camphora* EOs had an important antibacterial potency against *E. coli* with a MIC and MBC of 200 µg/L.

(Yap et al., 2015) have studied the EO of *C. verum* bark against *E. coli* by testing the permeability of its outer membrane, and they found that the observed membrane damage was determined by denaturation and acidification of the cell membrane (Borges et al., 2013). This suggested that the EO of *C. verum* bark disrupts the cell membrane at lethal and sub-lethal concentrations by increasing the availability of the antibiotic in the bacterial cell (Eumkeb et al., 2012). Indeed, EOs are complexes of antibacterial agents including natural aromatic and volatile compounds (Loy et al., 2001).

Antidiabetic Activities

Diabetes mellitus is a chronic disease that affects about 7% of the world's people (Zimmet et al., 2001) and it is expected to increase by 5.5% in 2025 (King et al., 1998). Diabetes mellitus type 2 (T2DM) accounts for 85–90% of all diagnosed diabetic patients (Wild et al., 2004) with high medical and social costs. Diabetes mellitus is characterized by an altered metabolism (of carbohydrates, lipids, and lipoproteins) and chronic hyperglycemia resulting from pancreatic β-cell dysfunction (Wild et al., 2004; Qin et al., 2010), insulin production deficiency, insulin resistance in key target tissues and impaired glycemic index control (Leiter and Lewanczuk, 2005), (DeFronzo et al., 1992). These alterations cause severe complications in the functioning of the cardiovascular system, as well as hypertension and dyslipidemia that are risk factors for stroke and myocardial infarction (Luscher and Steffel, 2008). Postprandial glucose control is essential for treating diabetes mellitus and avoiding its complications (Ortiz-Andrade et al., 2007). Moreover, correct diet and sport are necessary for the prevention of T2DM (Kahn et al., 2006; Hu, 2011).

TABLE 2 | Preclinical pharmacological activities of *Cinnamomum* genus.

Pharmacological activity	Cinnamum plant/extracts/ fractions	Methods	Models cellular lines (*in vitro*)/animal (*in vivo*)	Effects/underlying mechanisms	Ref
Antimicrobial	*Cinnamomum altissimum*/stem bark/EOs	Disk diffusion	MRSA	IC_{50} = 12.0 mm ↓bacterial growth	Buru et al. (2014)
		Microdilution	MRSA	IC_{50} = 156.25 μg/ml ↓ bacterial growth	
	Cinnamom umbejolghota/leaves/EOs	Disk diffusion	*Escherichia coli*	19.5 mm	Wannissorn et al. (2005)
			Salmonella saintpaul	17.5 mm	
			Salmonella derby	16.5 mm	
			Salmonella gallinarum	34 mm	
			Salmonella schwarzergrund	16.5 mm	
			Salmonella mbandaka	18 mm	
			Salmonella monterideo	16.5 mm	
	Cinnamom umburmanni Leaves/EOs	Microdilution	*Staphylococcus aureus*	IC_{50} > 2,500 μg/ml	Shan et al. (2007)
			Listeria monocytogenes	IC_{50} > 2,500 μg/ml	
			Salmonella anatum	IC_{50} > 2,500 μg/ml	
			Escherichia coli	IC_{50} > 2,500 μg/ml	
	Cinnamomum cassia leaves/EOs	Microdilution	*Pseudomonas putida*	IC_{50} = 500 mg/L	Oussalah et al. (2006)
	Cinnamomum cassia leaves/EOs	Microdilution	*Bacillus cereus*	IC_{50} = 500 mg/L	Turgis et al. (2012)
			Escherichia coli	IC_{50} = 500 mg/L not determined	
			Staphylococcus aureus		
	Cinnamomum cassia/shoots/ methanol	Disk diffusion Microdilution	*Escherichia coli*	13 mm IC_{50} = 250–500 μg/ml	Kim et al. (2004)
	Cinnamomum cassia bark/EOs	Disk diffusion Microdilution	*Listeria monocytogenes*	22.4 mm IC_{50} = 0.03 μg/ml	de Oliveira et al. (2012)
		Agar disc diffusion	*Bacillus subtilis*	21.1 mm	(Huang et al., 2014)
			Salmonella typhimurium	14.5 mm	
			Staphylococcus aureus	27.5 mm	
		Microdilution	*Staphylococcus aureus*	IC_{50} = 2.5–5 mg/ml	
		Microdilution assay	*Bacillus subtilis*	IC_{50} = 10 mg/ml	
			Salmonella typhimurium	IC_{50} = 20 mg/ml	
			Escherichia coli	IC_{50} = 10 mg/ml	
		Permeability of cell membrane	*Staphylococcus aureus*	↑ permeability of wall cell	
			Escherichia coli		
	Cinnamomum chemungianum leaves/EOs	Disk diffusion	*Staphylococcus aureus*	7 mm	Rameshkumar et al. (2007)
			Bacillus subtilis	8 mm	
			Salmonella typhi	9 mm	
			Escherichia coli	12 mm	
			Pseudomonas fluorescens	7 mm	
			Proteus vulgaris	7 mm	
			Klebsiella pneumoniae	11 mm	
	Cinnamomumim pressicostatum stem bark/VO	Disk diffusion Microdilution	MRSA	14.5 mm IC_{50} = 156.3 μg/ml	Buru et al. (2014)
	Cinnamomum iners stem bark/VO	Disk diffusion Microdilution	MRSA	10.5 mm IC_{50} = 625.0 μg/ml	Buru et al. (2014)
	Cinnamomum longepaniculatum leaves/VO	Microdilution	*Escherichia coli*	IC_{50} = 3.1 μL/ml	Li et al. (2014)
			Salmonella enteritidis	IC_{50} = 6.3 μL/ml	
			Staphylococcus aureus	IC_{50} = 6.3 μL/ml	
	Cinnamomummicranthum leaves/EOs	Diffusion method	*Vibrio parahemolyticus*	2 mm	Yeh et al. (2009)
			Vibrio alginolyticus	3 mm	
			Vibrio alginolyticus	3 mm	
			Vibrio vulnificus	2 mm	
			Lactococcus garvieae	1 mm	
			Debaryomyces hansenii	1 mm	
			Photobacteria damsel	1 mm	
			Streptococcus sp	1 mm	
			Eromonas hydrophila	2 mm	
	Cinnamomum micranthum twig/EOs	Diffusion method	*Vibrio parahemolyticus*	5 mm	
			Vibrio alginolyticus	5 mm	
			Vibrio alginolyticus	6 mm	
			Vibrio vulnificus	5 mm	
			Lactococcusgarvieae	3 mm	
			Debaryomyces hansenii	4 mm	
			Photobacteria damsel	7 mm	
			Streptococcus sp	7 mm	
			Eromonas hydrophila	1 mm	
	Cinnamomum osmophloeum leaves/EOs	Microdilution	*Escherichia coli*	IC_{50} = 250 μg/ml	Chang et al. (2001),
			Enterococcus faecalis	IC_{50} = 250 μg/ml	Chang et al. (2008)
			Klebsiella pneumoniae	IC_{50} = 500 μg/ml	

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TABLE 2 | (*Continued*) Preclinical pharmacological activities of *Cinnamomum* genus.

Pharmacological activity	Cinnamum plant/extracts/ fractions	Methods	Models cellular lines (*in vitro*)/animal (*in vivo*)	Effects/underlying mechanisms	Ref
			Salmonella sp	IC_{50} = 500 μg/ml	
			Vibrio parahemolyticus	IC_{50} = 250 μg/ml	
			Staphylococcus epidermidis	IC_{50} = 250 μg/ml	
			MRSA	IC_{50} = 250 μg/ml	
			Legionella pneumophila	IC_{50} = 1,000 μg/ml	
	Cinnamomum porrectum stem bark/VO	Disk diffusion	MRSA	7.5 mm	Buru et al. (2014)
		Microdilution		IC_{50} = 500 μg/ml	
	Cinnamomum tamala stem bark/ methanolic extract	Agar well diffusion	*Escherichia coli*	Without inhibition	Goyal et al. (2009)
			Salmonella typhi	11 mm	
			Bacillus cereus	14 mm	
			Bacillus subtilis	14 mm	
			Staphylococcus aureus	20 mm	
			Streptococcus pyogenes	13.5 mm	
			Staphylococcus aureus	IC_{50} = 256 μg/ml	
			Streptococcus pyogenes	IC_{50} = 4,096 μg/ml	
			Bacillus subtilis	IC_{50} = 4,096 μg/ml	
	Cinnamomum verum bark/EOs	Microdilution	*Staphylococcus aureus*	IC_{50} = 0.55 mg/ml	Unlu et al. (2010)
			Streptococcus pyogenes	IC_{50} = 0.55 mg/ml	
			Streptococcus pneumoniae	IC_{50} < 0.04 mg/ml	
			Enterococcus faecalis	IC_{50} = 1.15 mg/ml	
			Enterococcus faecium	IC_{50} = 1.12 mg/ml	
			Bacillus cereus	IC_{50} = 0.56 mg/ml	
			Acinetobacter lwoffii	IC_{50} < 0.04 mg/ml	
			Enterobacter erogenes	IC_{50} = 0.56 mg/ml	
			Escherichia coli	IC_{50} = 1.12 mg/ml	
			Klebsiella pneumoniae	IC_{50} = 0.14 mg/ml	
			Proteus mirabilis	IC_{50} = 0.14 mg/ml	
			Pseudomonas eruginosa	IC_{50} = 0.28 mg/ml	
			Salmonella typhimurium	IC_{50} = 0.14 mg/ml	
			Mycobacterium smegmatis	IC_{50} = 0.07 mg/ml	
			Clostridium perfringens	IC_{50} = 0.14 mg/ml	
			Listeria ivanovii	IC_{50} = 0.56 mg/ml	
			Listeria innocua	IC_{50} = 0.28 mg/ml	
			Listeria welshimeri	IC_{50} = 0.56 mg/ml	
			Listeria seeligeri	IC_{50} = 0.56 mg/ml	
	Cinnamomum verum bark/aqueous	Disk diffusion	*Moraxella cattarhalis*	11 mm	Rasheed and Thajuddin. (2011)
		Microdilution	*Moraxella cattarhalis*	IC_{50} = 120 mg/ml	
	Cinnamomum verum bark/EOs	Microdilution	*Pseudomonas eruginosa*	IC_{50} = 0.1125 mg/ml	Utchariyakiat et al. (2016)
	Cinnamomum verum bark/methanolic	Disk diffusion	*Proteus mirabilis*	5 mm	Hameed et al., (2016)
			Pseudomonas eurogenosa	4 mm	
			Escherichia coli	5.4 mm	
			Klebsiella pneumonia	6 mm	
			Staphylococcus aureus	5.2 mm	
	Cinnamomum verum bark/EOs	Microdilution	*Acinetobacter* spp.	IC_{50} = 625 μg/ml	Guerra et al., (2012), Noudeh et al., (2010)
			Staphyllococcus aureus	IC_{50} = 0.2 mg/ml	
			Bacillus subtilis	IC_{50} = 0.4 mg/ml	
			Escherichia coli	IC_{50} = 0.1 mg/ml	
			Pseudomonas eruginosa	IC_{50} = 0.2 mg/ml	
			Agrobacterium tumefaciens	IC_{50} = 12.5 mg/ml	
		Disk diffusion	*Staphylococcus aureus*	17.2 mm	Al-Bayati and Mohammed, (2009)
			Bacillus cereus	18.3 mm	
			Escherichia coli	15.7 mm	
			Proteus mirabilis	15.2 mm	
			Klebsiella pneumonia	17.5 mm	
			Pseudomonas eruginosa	14.4 mm	
			Staphylococcus aureus	IC_{50} = 62.5 μg/ml	
			Bacillus cereus	IC_{50} = 1.2 μg/ml	
			Escherichia coli	IC_{50} = 62.5 μg/ml	
			Proteus mirabilis	IC_{50} = 125.0 μg/ml	
			Klebsiella pneumonia	MIC = 62.5 μg/ml	
			Pseudomonas eruginosa	MIC = 125.0 μg/ml	
		Membrane permeability reduction test	*Escherichia coli*	↓wall cell permeability	Yap et al. (2015)
		Microdilution	*Pseudomonas putida*	IC_{50} = 1 mg/ml	Oussalah et al. (2006)

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TABLE 2 | (*Continued*) Preclinical pharmacological activities of *Cinnamomum* genus.

Pharmacological activity	Cinnamum plant/extracts/ fractions	Methods	Models cellular lines (*in vitro*)/animal (*in vivo*)	Effects/underlying mechanisms	Ref
Antidiabetic	***In vitro* studies**				
	Cinnamomum verum bark/aqueous	α-amylase, *a*-glucosidase inhibition		IC_{50} = 0.5, 1.25, 2.5 mg/ml ↓α-amylase, ↓α-glucosidase	Ranilla et al. (2010)
	Cinnamomum verum bark/methanol	Yeast *a*-glucosidase, rat-intestinal *a*-glucosidase inhibition		IC_{50} = 5.83 μg/ml ↓yeast *a*-glucosidase IC_{50} = 670 μg/ml ↓mammalian *a*-glucosidase	Shihabudeen et al. (2011)
	Cinnamomum cassia (L.) J. Presl/Bark/ acetone and aqueous	Glucosidase, sucrase, maltase inhibition		↓α-glucosidase inhibitory activity ↑ sucrase and maltase inhibition	Kang et al. (2014)
	Cinnamomum osmophloeum twig/ aqueous	PTP1B, *a*-glucosidase,α-amylase inhibition		↓ *a*-amylase, ↓α-glucosidase ↓ PTP1B	Lin et al. (2016)
	***In vivo* studies**				
	Cinnamomum burmanni (nees and T. Nees) blume/bark/aqueous	Rats/very high fat diet induced hyperglycemia 500, 300 mg/b.w.; oral		↓FBG, dose dependent manner	Cheng et al. (2012)
	Cinnamomum cassia (L.) J. Presl/bark/ aqueous	Rats/glucose 2 g/kg b.w. *ip*; 85.7 mg/b.w oral		↓blood glucose control: Glibenclamide	Verspohl et al. (2005)
	Cinnamomum cassia (L.) J.Presl/ aqueous	Mice/STZ induced diabetes; 100 mg/kg/day; oral		↓blood glucose ↑insulin	Chen et al. (2013)
	Cinnamomum cassia (L.) J.Presl/Bark/ Methanol	Mice/STZ induced diabetes; 200 mg/b.w.; oral		↓ blood glucose	Kim et al. (2006)
	Cinnamomum cassia (L.) J. Presl bark/ aqueous	Rats/alloxan induced diabetes 60 mg/b.w.; oral		↓blood glucose	Kamble and Rambhimaiah, (2015)
	Cinnamomum porrectum bark/ polyphenols rich extract	Rats/STZ induced diabetes 100,200,300 mg/b.w.; oral		↓blood glucose	Jia et al. (2009)
	Cinnamomum tamala/leaves/ethanol	Rats/alloxan induced diabetes; 500 mg/b.w.; oral		↓ blood glucose	Kar et al. (2003)
	Cinnamomum tamala leaves/ essential oil	Rats/STZ induced diabetes 10, 200 mg/b.w.; oral		↓ blood glucose	Kumar et al. (2012)
	Cinnamomum verum bark/water-soluble polyphenols	Rats/STZ induced diabetes 200 mg/kg, oral		↑weight loss ↓FBG, ↓PPG	Krishnakumar et al. (2014)
	Cinnamomum verum bark/volatile oil	Rats/STZ induced diabetes 20 mg/kg; oral		↓plasma glucose	Subash Babu et al. (2007)
	Cinnamomum verum essential oil	Rats/STZ induced diabetes 20 mg/kg; oral		↓blood glucose	Al-Logmanil and Zari, (2009)
	Cinnamomum verum stem bark/ chloroform	Rats/STZ induced diabetes 20 mg/kg; oral		↑muscle glycogen ↑hepatic glycogen ↓FBG	Anand et al. (2010)
	Cinnamomum verum bark/volatile oil	Rats/alloxan induced diabetes 5, 10, 20 mg/kg; oral		↓FBG, dose-dependent manner ↓cholesterol ↓urinary protein ↓TBARS ↓blood urea ↓catalase	Mishra et al. (2010)
	Cinnamomum verum bark/volatile oil	Rats/alloxan induced diabetes 5, 10 and 20 mg/kg; oral		↓FBG, dose-dependent manner	Rajbir et al. (2009)
	Cinnamomumverum sticks/Aqueous	Rats/STZ induced diabetes 3, 30 and 100 mg/kg; oral		↓blood glucose, dose-dependent manner	Shen et al. (2010)
	Cinnamomumverum bark/aqueous	Rats/oral glucose tolerance test 0.2 ml day/rat; oral		↓glycemic levels	Kannappan et al. (2006)
	Cinnamomum verum/bark/methanol	Rats/STZ induced diabetes 300 mg/kg; oral		↓ postprandial hyperglycemia	Shihabudeen et al. (2011)
Anti-inflammatory	***In vitro* studies**				
	Cinnamomum cassia/cinnamic aldehyde	RAW 264.7, LPS stimulated mice macrophages		$IC_{50=}$ 0, 6.25, 12.5, 25, 50 μM anti-inflammatory	Liao et al. (2012a)
	Cinnamomum camphora/total crude extract/80% methanol, hexane, ethyl acetate fractions	RAW 264.7, LPS stimulated mice macrophages		$IC_{50=}$ 100 μg/ml anti-inflammatory	Lee et al. (2006)
	***In vivo* studies**				
	Cinnamomum cassia bark oil/ cinnamaldehyde	Rats		dose = 2–6 mg/kg bw ↓NF-kB	Chua et al. (2008)
	Cinnamomum cassia cinnamic aldehyde	Mice/carrageenan induced paw edema		dose = 1.25, 2.5, 5 mg/kg/bw Anti-inflammatory	Liao et al. (2012a)

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TABLE 2 | (*Continued*) Preclinical pharmacological activities of *Cinnamomum* genus.

Pharmacological activity	Cinnamum plant/extracts/ fractions	Methods	Models cellular lines (*in vitro*)/animal (*in vivo*)	Effects/underlying mechanisms	Ref
Anti-cancer	***In vitro* studies**				
	C. burmanni stem bark/methanolic	NPC/HK1, C666–1, human cancer cell lines		↑cytotoxicity IC_{50} = 224.3 μg/ml IC_{50} = 6.30 μg/ml	Daker et al. (2013)
	C. cassia bark aqueous	SiHa, human cervical carcinoma cell lines		↓growth of cancer cells ↑cytotoxicity IC_{50} = 80 μg/ml	Koppikar et al. (2010)
	C. cassia ethanolic extract	HT 29, HCT 116, human colorectal carcinoma cell lines		↑Nrf2 ↑antioxidant	Wondrak et al. (2010)
	C. burmann stem bark/aqueous	Lymphoma, melanoma, mice cancer cell lines		↓tumor cell growth ↑cytotoxicity IC_{50} = 0.5 mg/ml	Kwon et al. (2010)
	Cinnamomum species cinnamaldehyde	Hep G2, hepatoma cells line		↑apoptosis ↑p53, ↑APO-1 ↑cytotoxicity IC_{50} = 9.8 μM	Ng and Wu. (2011)
	C. subavenium miq subamolide D subamolide E	SW 480, human colon adenocarcinoma cell lines A431, SCC1 human epidermoid carcinoma cells A375, human melanoma cell lines		↑DNA damage ↑cytotoxicity IC_{50} = 9.12 μg/ml IC_{50} = 13.30 μg/ml IC_{50} = 17.59 μg/ml	Kuo et al. (2008); Yang et al. (2013)
	C. subavenium miq subamolide B, A	NTUB1, human urothelial carcinoma cell line SW480, human colon adenocarcinoma cell line		↓tyrosinase ↑apoptosis	Chen et al. (2007); Wang et al. (2011)
	C. tenuifolium/butanolides	DU145, human prostate cancer cell line		↓mitochondrial transmembrane potential ↑cytochrome C ↑caspase-9/caspase-3 ↑cytotoxicity	Lin et al. (2009)
Neuroprotective	***In vitro* studies**				
	Cinnamomum species water extract/ procyanidin type a trimer	C6 glial cells, OGD exposed		↓glial cell swelling ↓glutamate uptake	Panickar et al. (2012)
	Cinnamomum cassia/extract/ cinnamaldehyde	BV2 microglias, LPS activated		↓neuroinflammation IC_{50} = 50 μg/ml	Ho et al. (2013)
	***In vivo* studies**				
	Cinnamomum species *trans*-cinnamaldehyde	Mice/6-OHDA treated intracerebroventricular		Anti-neuroinflammatory Dose = 30 mg/kg	Pyo et al. (2013)
	Cinnamomum zeylanicum bark extract	Rats/SCOP treated intravenous		↑cognition dose = 100, 200, 400 mg/kg	Jain et al. (2015)
Others pharmacological activities	***In vivo* studies**				
	Cinnamomum zeylanicum/stem bark/ methanol extract	Rats/L-name-induced hypertension, intravenous		Antihypertensive dose = 5, 10, 20 mg/kg	Nyadjeu et al. (2011)
	Cinnamomum zeylanicum/bark and leaf/EOs	*Culex quinquefasciatus, Anopheles tessellatus* and *Aedes egypti*		Mosquitocidal Bark oil *A. essellatus* LD_{50} = 0.33 μg/ml *C. uinquefasciatus* LD_{50} = 0.66 μg/ml leaf oil LD_{50} = 1.03–2.1 μg/ml	Samarasekera et al. (2005)
	Cinnamomum zeylanicum bark/EOs	*Pediculushumanus capitis*		Ovicidal, adulticidal activities LD_{50} = 0.5 mg/cm^2	Yang et al. (2005)
	Cinnamomum zeylanicum bark/ aqueous suspension	Rats		Anti-secretagogue Antiulcer dose = 250, 500 mg/kg b.w	Alqasoumi. (2012)
	Cinnamomum zeylanicum bark/ ethanol extract	Rats		Pro-healing effect dose = 250, 500 mg/kg b.w	Kamath et al. (2003); Farahpour and Habibi. (2012)
	Cinnamomum zeylanicum bark/ ethanol extract	Rats/CCl_4-induced liver injury		↑hepatoprotective Dose = 0.01, 0.05, 0.1 g/kg	Eidi et al. (2012)

Abbreviations and symbols: ↑, increase; ↓, decrease; APOA-1, Apolipoprotein A-1; bw, body weight; FBG, fasting blood glucose; L-NAME, N(G)-nitro-L-arginine-methyl ester, LPS, lipopolysaccharide; p53, tumorprotein p53; PPG, postprandial plasma glucose; PTP1B, protein-tyrosine phosphatase; NF-κB, nuclear factor κB; OGD, oxygen-glucose deprivation; 6-OHDA, 6-hydroxydopamine; SCOP, scopolamine; STZ, streptozotocin; TBARS, thiobarbituric acid reactive substances.

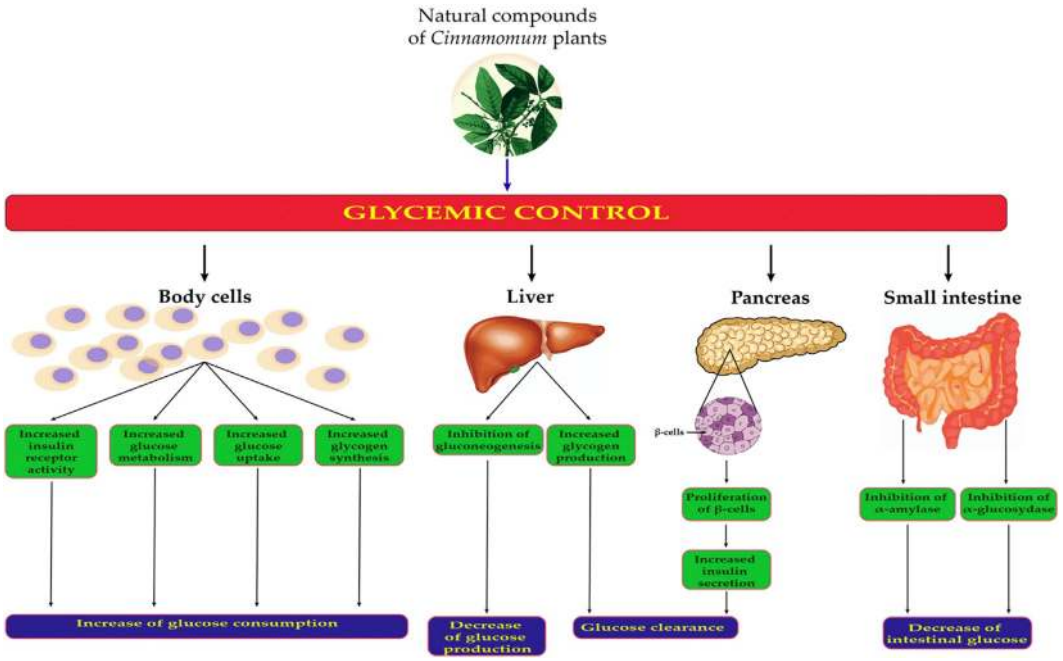

FIGURE 3 | Potential mechanisms of antidiabetic effects of chemical compounds of *Cinnamomum* plants. Body cells mean all the human cells with receptors for insulin.

The antidiabetic mechanisms of natural compounds derived from *Cinnamomum* spp. are explained as follow: 1) stimulation of insulin secretion by pancreatic β-cells of the islets of Langerhans, 2) increasing the muscle and hepatic glycogen content, 3) inhibition of α-amylase and α-glucosidase activities (key enzymes of carbohydrate metabolism) (Subash Babu et al., 2007; Zhang et al., 2008) 4) stimulation of glycogen synthesis and cellular glucose uptake by membrane translocation of glucose transporter (GLUT 4); stimulation of the glucose metabolism, 5) reduction of the gluconeogenesis by its actions on the most important regulatory enzymes, 6) potentiation of insulin release and increasing insulin receptor activity (Bandara et al., 2012; Ranasinghe et al., 2012). (**Figure 3)** and **Table 2**.

The antihyperglycemic action of the soluble polyphenols of *C. verum* bark was verified in SZT-induced diabetic rats at the dose of 200 mg/body weight (Krishnakumar et al., 2014). Cinnamaldehyde isolated from the volatile oil of *C. verum* showed a highly significant effect on plasma glucose levels using a rat model of SZT-induced diabetes (Subash Babu et al., 2007). This major component has a wide variety of pharmacological properties, including antihyperglycaemic activity in diabetic rats (Subash Babu et al., 2007; Zhang et al., 2008). Al-LogmaniI and Zari (2009) have also tested the EO of *C. verum* and showed an important reduction in blood sugar levels.

The chloroform extract of *C. verum* bark stem exhibited antidiabetic activity *in vivo* at 20 mg/body weight using a rat model of SZT-induced diabetes (Anand et al., 2010). The authors demonstrated that the chemical compounds of extract increased the muscle and liver glycogen content. By using alloxan-induced diabetes in rats, other studies showed that the EO of *C. verum* bark decreased fasting blood sugar in a dose-dependent manner and reduced total cholesterol level, blood urea, urinary protein, thiobarbituric acid reactive substances (TBARS), and catalase levels in diabetic rats (Rajbir et al., 2009; Mishra et al., 2010). A few studies have reported the antidiabetic effect of *C. verum* aqueous extracts (Verspohl et al., 2005; Kannappan et al., 2006; Ranilla et al., 2010; Shen et al., 2010; Chen et al., 2013).

The antihyperglycemic activity can also be evaluated by the inhibition test of α-glucosidase and α-amylase. Inhibitors of these enzymes are intended to maintain glucose homeostasis in diabetics by decreasing the rate of glucose uptake (Bösenberg and van Zyl, 2008; Hanhineva et al., 2010). (Ranilla et al., 2010) showed an important inhibition of α-glucosidase and α-amylase actions by *C. verum* bark aqueous extract. The same extract attenuated hyperglycemia depending on the dose in SZT diabetic rats (Shen et al., 2010; Chen et al., 2013). The antidiabetic effect of this extract was confirmed by the decrease in blood glucose using oral glucose tolerance test in rats (Kannappan et al., 2006; Chen et al., 2013).

In an *in vitro* study, *C. verum* showed a potential antidiabetic effect by reducing post-prandial intestinal glucose absorption via enzymatic reduction of pancreatic α–amylase and intestinal α–glucosidase. *In vivo* studies also confirmed the anti-hyperglycemic effects of *C. verum* (Bandara et al., 2012; Ranasinghe et al., 2012) through the decrease in LDL cholesterol, total cholesterol and triglycerides with increasing HDL in hyper-lipidaemic albino rabbits. (Javed et al., 2012).

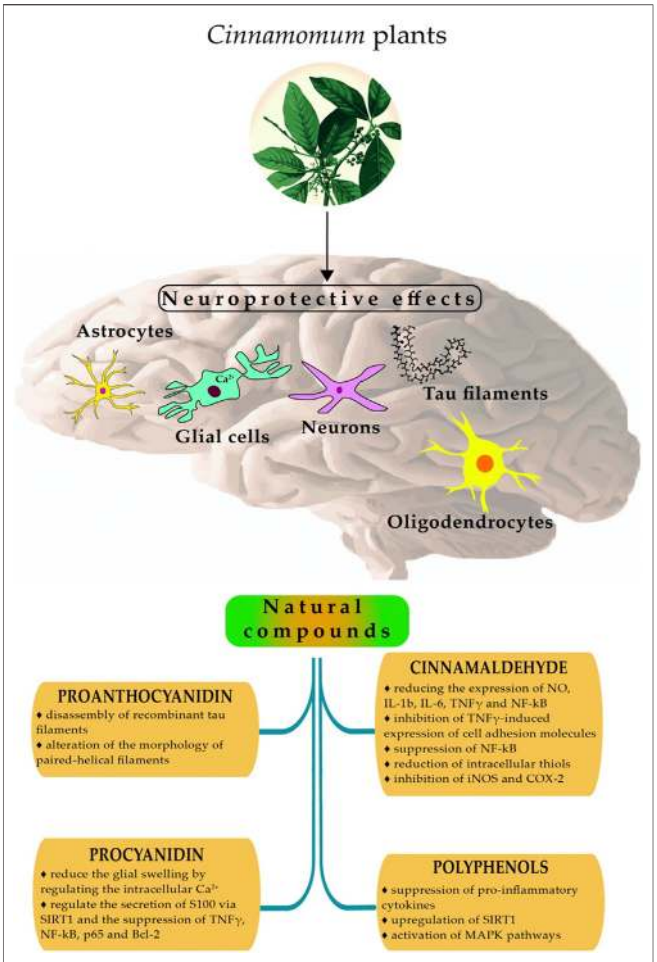

FIGURE 4 | Summarized mechanisms of neuroprotective effects of Cinnamomum plants. Abbreviations: SIRT1, Sirtuin 1; MAPK, mitogen-activated protein kinase; iNOS, inducible Nitric Oxide synthase; TNF-γ, tumor necrosis factor; COX-2, Cyclooxygenase-2; NF-kB, Nuclear Factor-Kappa B; p65 (RelA subunit of NF-κB family of transcription factors); Bcl-2, B-cell lymphoma 2; IL-1b, Interleukin-1beta; IL-6, Interleukin 6.

Antioxidant Activity

Some clinical investigations showed that long term consumption of cinnamon extracts improved the levels of blood markers of oxidative stress, such as the antioxidant capacity. The extracts also reduced the transaminase and lipid peroxidase activities (Ranjbar et al., 2007; Rashidi et al., 2014). Diverse tests were used to evaluate potential antioxidant action of *Cinnamomum* plant extracts and secondary metabolites. These include 2,2′-azinobis (3-ethyl-benzothiazoline-6-sulphonic acid (ABTS), 2,2-diphenyl-1-picrylhydrazyl (DPPH), ferric reducing antioxidant power (FRAP), oxygen radical absorbance capacity (ORAC), Folin Ciocalteau reduction assay (FCR), β carotene linoleic acid bleaching (BCLB), and enzyme inhibition assays.

The antioxidant activity of *C. osmophloeum* leaf EOs was assessed using DPPH radical scavenging assay, with IC_{50} = 29.7 μg/ml (Lin et al., 2007). The ethanol extract of the same species was tested using DPPH and FRAP assays by (Lee et al., 2015). The results showed inhibitory values of 38.97 and 0.48% by DPPH and FRAP test, respectively.

(Prasad et al., 2009) tested the antioxidant activity of ethanolic extract of *Cinnamomum curvifolium* (Lam.) Nees, *C. burmanni, C. cassia, C. verum,* and *C. tamala* using DPPH, FRAP and ORAC assays. All tested species showed important antioxidant activities with some variability depending on the species and the used method (Prasad et al., 2009). *C. cassia* was also reported as an antioxidant species by several studies (Lin et al., 2003; Kim et al., 2006; Jang et al., 2007). *C. cassia* water extract showed important capacities to inhibit the key enzymes involved in ROS generation such as catalase, superoxide dismutase and glutathione peroxidase (Kim et al., 2006). Methanolic extract of *C. verum* revealed remarkable antioxidant activities particularly by chelating metal and inhibition of lipid peroxidation (Mathew and Abraham, 2006). Moreover, the inhibition of lipid peroxidation was also demonstrated by EOs of *C. verum* (Jayaprakasha et al., 2003; Jayaprakasha et al., 2006). The research that highlighted the antioxidative activity of *Cinnamomum* plants is summarized in **Table 2**.

Anti-inflammatory Activities

Inflammation is an important pathophysiological process of the organism that maintains homeostasis, fighting pathogens and repairing damaged tissues caused by various injuries such as trauma, infection or immune response (Salehi et al., 2019b), (Stalnikowitz and Weissbrod, 2003). The same inflammatory process is involved in the maintenance of several disorders and is characterized by the production of diverse pro-inflammatory mediators (Salehi et al., 2020a). The current common class of medications against inflammation disorders still relies on non-steroidal anti-inflammatory drugs (Padureanu et al., 2019). However, in spite of having important anti-inflammatory potential, these drug class can cause several side effects such as bleeding, kidney failure and gastrointestinal ulceration. Therefore, increasing attention has been directed towards natural and health-friendly alternatives (Salehi et al., 2019c; Salehi et al., 2019d). The use of natural compounds constitutes an attractive approach for the treatment of several inflammatory disorders.

Inflammation involves reactive oxygen species (ROS) generation, NO production, phospholipase A_2 activation and histamine release in neutrophils, macrophages and mast cells. NO has an important role in lipopolysaccharide (LPS), TNF or IL-1 mediated inflammatory process. It is also essential in the cell function maintenance (Stalnikowitz and Weissbrod, 2003) though, on the other hand, NO is able to induce cell injury as a reactive radical. The activator protein-1 (AP-1) and nuclear factor kappa B (NF-kB) are important modulators of inflammation.

The main mechanism of the anti-inflammatory activity of the major chemical compound of *Cinnamomum* plants, cinnamaldehyde is the effective inhibitor of the expression of NF-kB mediated by its antioxidant activity (Kim et al., 2007). In addition, cinnamaldehyde inhibits pro-inflammatory mediators such as chemokines, interferons, interleukins, lymphokines, eicosanoids (prostaglandins and leukotrienes) and ROS involved in Alzheimer's disease (Latta et al., 2015). Preclinical

studies showed a reasonably good anti-inflammatory effect of *Cinnamomum* constituents. Diverse extracts and isolated compounds of *Cinnamomum* plants have been studied for possible anti-inflammatory activity in various animal models. (Liao et al., 2012b) showed an anti-inflammatory effect of cinnamaldehyde on lipopolysaccharide (LPS) stimulated mouse macrophage (RAW 264.7) at 50 μM.

The *in vivo* investigations confirmed the anti-inflammatory effect using the carrageenan-induced mouse paw edema (Liao et al., 2012b). Cinnamic alcohol (another volatile compound from *Cinnamomum* plants) also exerted anti-inflammatory activity using the same model (Liao et al., 2012b). In another study, cinnamyl acetate revealed a significant anti-inflammatory action on LPS-stimulated mouse macrophages (RAW264.7) (Chua et al., 2008). The research highlighting the anti-inflammatory activity of *Cinnamomum* plants is displayed in **Table 2**.

Anticancer Activities

Recent researches showed that the *in vivo* anticancer activity of the cinnamon extract was mediated by the induction of tumor apoptosis through the inhibition of NF-κB levels (Kwon et al., 2010). On the other hand, cinnamon showed important anti-cancer effects via affecting on numerous cancer-related pathways such as apoptosis (Kwon et al., 2010). This apoptotic action is mediated by targeting Fas/Fas/CD95, caspase-3, and Bcl-XL (B-cell lymphoma-extra-large) pathways (Sadeghi et al., 2019).

C. burmanni stem bark methanolic extract was tested on human cell lines (NPC/HK1 and C666-1) by Daker et al. (2013). The results showed important cytotoxic effect against HK1 (IC50 = 224.3 μg/ml) and C666-1 (IC50 = 6.30 μg/ml) Daker et al. (2013). Koppikar et al. (2010) tested the aqueous bark extract of C. cassia on human cervical carcinoma (SiHa) cell lines. This extract decreased the growth of cancer up to 2-fold compared to the untreated control cells at the concentration of 80 μg/ml Koppikar et al. (2010).

In another study, the ethanolic extract of the same species tested by Wondrak et al. (2010) on human colorectal carcinoma (HCT 116 and HT 29) cell lines showed anticancer properties. The *C. cassia* bark aqueous extract was evaluated on cancer cell lines of lymphoma, melanoma and cervix as well as in a melanoma mouse model (Kwon et al., 2010). The cinnamon extract inhibited tumor cell growth *in vitro* at 0.5 mg/ml.

Cinnamaldehyde showed an important antitumor effect as well (Ng and Wu, 2011). It inhibited the growth of hepatoma Hep G2 cells line at IC_{50} = 9.8 μM. Some bioactive compounds isolated from *Cinnamomum subavenium* Miq. such as subamolide D and E showed remarkable anticancer effects on human colon adenocarcinoma (SW 480) cell lines. The cytotoxic effect was mediated by the capacity of these compounds to cause DNA damage in a dose- and time-dependent manner (Kuo et al., 2008). Moreover, subamolide B isolated from the stem of the same plant showed significant cytotoxic effects on human SCC12 (IC_{50} = 9.12 μg/ml), epidermoid carcinoma A431 (IC_{50} = 13.30 μg/ml), and human melanoma A375 (IC_{50} = 17.59 μg/ml) cell lines (Yang et al., 2013).

In another study, subamolide B and its isomer subamolide A induced apoptosis in human colon adenocarcinoma cell line SW480 and human urothelial carcinoma cell line NTUB1(Chen et al., 2007; Wang et al., 2011). Furthermore, subamolide E, isolated from *C. subavenium,* exhibited an important *in vitro* anti-melanoma activity (Kuo et al., 2008; Wang et al., 2011). (Lin et al., 2009) reported that butanolides isolated from the stem of *Cinnamomum tenuifolium* (Makino) Sugim showed anticancer activity on human prostate cancer (DU145) cell line. (Lin et al., 2009). In addition, the extracts of *C. kotoense* was found cytotoxic against HeLa cells (Chen et al., 2008). Butanolides isolated from the *C. kotoense* leaves reported genotoxic and cytotoxic effects on various cell lines, such as human laryngeal carcinoma cells Hep-2, Chinese hamster ovarian cells CHO-K1 and rat hepatoma tissue cultures (Garcez et al., 2005) and mouse lymphoid leukemia P-388 cells (Tsai et al., 2002). *In vitro* antineoplastic activities of *Cinnamomum* species are summarized in **Table 2**.

Neuroprotective Activities: Potential Mechanisms and Molecular Targets in Neurodegenerative Diseases

Parkinson's and Alzheimer's diseases are common neurodegenerative diseases, accompanied by cognitive and memory impairments, sometimes difficult to differentiate from real psychosis or other neurological diseases (Nussbaum et al., 2017; Buga et al., 2019; Tsatsakis et al., 2019). The mechanisms of neuroprotective effects of *Cinnamomum* plants and their derivatives have been reported by several studies (Liao et al., 2008; Peng et al., 2008; Peterson et al., 2009; Panickar et al., 2012; Jiao et al., 2013). (**Figure 4**).

(Ho et al., 2013) showed that procyanidinA trimer 1 (a bioactive compound isolated from *C. burmanni*) had an essential neuroprotective effect which reduced the glial swelling by regulating the intracellular calcium concentration in glial neuronal cells (Peng et al., 2008). Procyanidin exhibited neuroprotective activity by its capacity to regulate the secretion of S100 via the regulation of SIRT1 and the suppression of TNF-γ, NF-kB p65 (RelA subunit of NF-κB family of transcription factors) and B-cell lymphoma 2 (Bcl-2) on glioma cells (Jiao et al., 2013).

(Panickar et al., 2012) studied the neuroprotection of procyanidin B2 isolated from *C. verum.* The results showed that this molecule inhibited advanced glycation end-product production in the bovine serum albumin-glucose model (Panickar et al., 2012).

Cinnamaldehyde is a volatile compound found in *C. cassia* extracts. (Ho et al., 2013) showed that this compound possessed an important neuroprotective effect by reducing the expression of NO, tumor necrosis factor (NF-γ), interleukin-1beta (IL-1b), interleukin 6 (IL-6), and nuclear factor-kappa B (NF-kB) in LPS induced BV2 microglia cells.

In a recent study, (Liao et al., 2008) revealed that cinnamaldehyde from *C. cassia* exhibited remarkable neuroprotection by the reduction of TNFγ-induced expression of cell adhesion molecules, the suppression of nuclear factor-kappa B (NF-kB) and the reduction of intracellular thiols in endothelial cells (Liao et al., 2008).

Cinnamaldehyde isolated from *C. ramulus* exhibited anti-neuro-inflammatory properties by the inhibition of inducible

TABLE 3 | Description of recent clinical studies related to pharmacological activity of natural compounds from *Cinnamomum* species.

Pharmacological activity	Clinical trial/study design (type, patients included)	Period, country	Intervention (doses of *Cinnamon* and its derivatives)	Standard comparison	The most representative clinical outcomes	Ref
Type 2 diabetes	Two groups included: Cinnamon- group 1,2, 3 Placebo- group 4, 5, 6 Cinnamon group: 60 patients Age 52.2 ± 6.32 years Not on insulin therapy Not taking other medicine Fasting blood glucose Levels 7.8–22.2 mmol/L	Department of Human Nutrition, NWFP Agricultural University, Peshawar, Pakistan	Cinnamon group: 500 mg capsule of *Cinnamomum cassia* placebo group: Wheat flour, 500 mg, 1 g or 2 capsules per day for 20 days; group 1 and 4: 3 g or 6 capsules per day for 20 days; group 2 and 5: 6 g or 12 capsules per day for 20 days; group 3 and 6; 6 g or 12 capsules per day for 40 days	Placebo	↓serum glucose (18–29%), ↓TG (23–30%), ↓LDL-C (7–27%) ↓total cholesterol (12–26%)	Khan et al. (2003)
Type 2 diabetes	Cinnamon group: 33 patients, age 62·8 ± 8·37 Body weight 88·5 ± 19·1 kg HbA1c 6.7–6.9% Placebo group: 32 patients age 63·7 ± 7·17 years Body weight 89·9 ± 14·1 kg HbA1c 6.7–6.9%	Hannover, Germany	Cinnamon group: Extract 112 mg aqueous cinnamon extract placebo: Microcrystalline cellulose 3 g powder per day, three times a day for 4 months	Placebo	↓glucose levels up to 10.3%	Mang et al. (2006)
Type 2 diabetes	Cinnamon group 12 postmenopausal women age 62 ± 2 years Body weight 85.4 ± 3.6 kg Placebo group: 13 patients Age 64 ± 2 years Body weight 82.2 ± 4.0 kg	Netherlands	Cinnamon group: 500 mg of *Cinnamomum cassia* placebo group: 500 mg, wheat flour, verstegen 1.5 g per day, 1 capsule at breakfast, lunch and dinner for 6 weeks	Placebo	↓plasma glucose, ↓plasma insulin, ↓total cholesterol, ↓LDL, ↓TG ↓HDL ↓HbA1c	Vanschoonbeek et al. (2006)
Type 2 diabetes	Cinnamon group: 30 patients Age 63.6 years Placebo: 22 patients Age 58.0 years	US	Cinnamon group: 500 mg capsule of *Cinnamomum cassia* placebo group: Wheat flour, 500 mg capsule: 1 g per day, for breakfast and dinner for 3 months	Placebo	No significant change in FBG, lipid for cinnamon group	Blevins et al. (2007)
Type 2 diabetes	Cinnamon group: 55 patients Age 60.5 ± 10.7 HbA1c ≥ 7.0% control group: 54 patients Age 59.9 ± 9.2 years HbA1c ≥ 7.0%	United States military base, May 2007 to August 2007	Cinnamon group: Capsules 500 mg capsule of *Cinnamomum cassia* control group: 1 g/day with food for 90 days	Control	Cinnamon group ↓ HbA1c	Crawford. (2009)
Multi-ethnic type 2 diabetic	Cinnamon group: 58 patients, age 54.9 ± 9.8 years Body weight 74.94 ± 13.34; FPG≥ 7 mmol/L HbA1c ≥ 7.0% placebo group: 22 patients Age 55.67 ± 7.98 years Body weight 73.02 ± 10.38 years FPG≥7 mmol/l HbA1c ≥ 7.0%	October 2007 to January 2009, United Kingdom	Cinnamon group: 500 mg capsule of *Cinnamomum cassia* placebo: Starch, 500 mg capsule 2 g per day, for breakfast (1 capsule), lunch (2 capsules), dinner (1 capsule) for 12 weeks	Placebo	↓HbA1c ↓FPG ↓BMI	Akilen et al. (2010)

(Continued on following page)

TABLE 3 | (*Continued*) Description of recent clinical studies related to pharmacological activity of natural compounds from *Cinnamomum* species.

Pharmacological activity	Clinical trial/study design (type, patients included)	Period, country	Intervention (doses of *Cinnamon* and its derivatives)	Standard comparison	The most representative clinical outcomes	Ref
Type 2 diabetes	Cinnamon group: 22 patients Age 54.11 ± 10.37 years Body weight 74.94 ± 13.34 Placebo group: 22 patients Age 55.67 ± 7.98 years Body weight 73.02 ± 10.38 kg	Tehran, Iran	Cinnamon group: 500 mg capsule of *Cinnamomum zeylanicum* placebo group: 500 mg capsule, wheat flour 3 g per day, 2 capsules at breakfast, lunch and dinner for 8 weeks	Placebo	No significant difference in cinnamon and placebo group on HbA1c, ↓TG, ↓Insulin ↑ LDL-C	Vafa et al. (2012)
Type 2 diabetes	Cinnamon group: 137 patients Age 61.3 ± 0.8 years	Beijing and dalian, China	Cinnamon group: Water extract of cinnamon and CinSulin®, 250 mg/capsule placebo: 500 mg capsule, wheat flour daily, twice a day for 2 months	Placebo	↓LDL-C ↓HDL ↓HOMA-IR	Anderson et al. (2015)
Type 2 diabetes	Cross-over study cinnamon group:10 sedentary obese females Age 22.7 ± 4 years Body weight 104.42 ± 16.75 kg Take oral/intrauterine contraceptives Prescription medications Over-the-counter weight loss pills	Texas, United States	Cinnamon group: 1–6 g/day powder of *C. cassia/ aromaticum* and *C. zeylanicum/verum* placebo: Cellulose powder 5 g	Placebo	No differences observed in blood glucose, serum insulin, insulin sensitivity, insulin resistance	Gutierrez et al. (2016)
Type 2 diabetes	Cinnamon group: 40 patients Age 54.15 ± 1.0 years Weight 75.62 ± 1.2 kg Control group:40 patients Age 53.64 ± 1.3 years Weight 78.74 ± 1.2 kg	September 2012 to December 2012, Iran	Cinnamon group*: Cinnamomum verum* 3 g for 8 weeks control group: 3 glasses of tea, for 8 weeks	Control	↓sICAM-1	Azimi et al. (2016)
Polycystic ovary syndrome	Herbal medicine plus lifestyle intervention study Cinnamon group: 60 overweight women Age 29.2 ± 5.6 years Weight 93.2 ± 18.9 kg Lifestyle intervention group: 62 patients age 28.9 ± 5.6 Weight 97.3 ± 21.3 kg	August 2012 to January 2014, Australia	*Glycyrrhiza glabra, Paeonia lactiflora, Cinnamomum verum, Hypericum perforatum:* three tablet per day for 3 months	Lifestyle intervention	↓ oligomenorrhoea ↓ BMI ↓ weight	Arentz et al. (2017)
Polycystic ovary syndrome	Cinnamon group: 29 patients Age 18–45 years Weight 68.24 ± 9.68 kg Placebo group: 30 patients Age 18–45 years 63.26 ± 11.62 kg	Iran	Cinnamon group: 500 mg capsules (450 mg capsule of starch and 50 mg cinnamon powder): 1.5 g per day three times, after a meal with 10 mg medroxyprogesterone tablet from 15th day of menstruation cycle for 10 days for 12 weeks	Placebo	↓fasting insulin, ↓HOMA-IR, ↓LDL, ↓TG, ↓testosterone, ↓ insulin, ↓ weight ↓HbA1c	Hajimonfarednejad et al. (2018a)

(Continued on following page)

TABLE 3 | (*Continued*) Description of recent clinical studies related to pharmacological activity of natural compounds from *Cinnamomum* species.

Pharmacological activity	Clinical trial/study design (type, patients included)	Period, country	Intervention (doses of *Cinnamon* and its derivatives)	Standard comparison	The most representative clinical outcomes	Ref
Polycystic ovary syndrome	Cinnamon group: 42 patients with rotterdam criteria Age 29.26 years Placebo group: 42 patients with rotterdam criteria Age 30 years	september 2015 to januray 2016, tehran, Iran	Cinnamon group: 500 mg capsule/day placebo: Wheat flour: 1.5 g per day for 8 weeks	Placebo	↑antioxidant capacity ↓malondialdehyde↓ BMI	Borzoei et al. (2018a)
Polycystic ovary syndrome	Cinnamon group: 42 patients with rotterdam criteria Age 29.3 years Weight 76.6 kg Placebo group: 42 patients with rotterdam criteria Age 30.2 years Weight 77.7 kg	Mohheb Yas Hospital, Tehran, Iran, October 2015 to February 2016	Cinnamon group: 500 mg capsule/day placebo: Wheat flour: 1.5 g per day for 8 weeks	Placebo	↓TG, ↓BMI, ↓TC ↓HOMA-IR ↓insulin, ↓ LDL-C HDL-C unchanged	Borzoei et al. (2018b)
Polycystic ovarian syndrome	Cinnamon group 11 patients, age 18–38 years with oligomenorrhea or amenorrhea Placebo group: 6 patients Age 18–38 years	March 2011 to April 2014 to United States	Cinnamon (125 mg capsule) or placebo: 1.5 gm per day for 6 months	Placebo	↑ homa-ir	Kort and Lobo. (2014a)
Polycystic ovarian syndrome	DLBS3233: 18 patients Metformin group: 22 patients	March 2013 and June 2015 at yasmin clinic, RSCM kencana, jakarta and hasan sadikin hospital, bandung	DLBS3233 (*Cinnamomum burmanii* and *Lagerstroemia speciosa*): 200 mg per day for 6 months metformin group: 1.5 g per day for 6 months	Control	↓AMH level	Wiweko and Susanto. (2017)
Polycystic ovarian syndrome	Patients age 23.29 ± 5.10 with rotterdam, overweight or obese	Saudi Arabia	Cinnamon extract (336 mg/day)	Placebo	↓BMI	Talaat and Ammar, (2018)
Polycystic ovary syndrome	40 patients age 18–30 years	2017, ahvaz, Iran	6 weeks	Intervention group	↓weight glucose homeostasis no effects	Parseh et al. (2019)
Polycystic ovary syndrome	Cinnamon group: 20 patients, age 18–42 years with rotterdam criteria	December 2014 to March 2016, national institute of unani medicine (NIUM) hospital, Bengaluru	Cinnamon group: 750 mg capsule,1.5 g/day control group: 500 mg metformin twice a day for 60 days	Control	Menstrual cycle inprovment increased 51.9%, insulin resistance unchanged	Khan and Begum. (2019)

nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2) in LPS-induced BV2 microglial cells (Pyo et al., 2013).

In addition, cinnamon bioactive compounds exhibited neuroprotective effects in *in vivo* models of Alzheimer's disease and extended the lifespan via regulation of key antioxidant pathways (Crews et al., 2016). *C. verum* extracts provided an important protection against Alzheimer's disease and dementia in the scopolamine-induced memory impairment in experimental rat model (Jain et al., 2015).

In the same way, a different mixture of cinnamon rich in polyphenols exhibited important neuroprotective activities in rat glioma cells by suppression of pro-inflammatory cytokines, upregulation of sirtuin 1 (SIRT1) and activation of mitogen-activated protein kinase (MAPK) pathways (Qin et al., 2014). Neuroprotective activities of *Cinnamomum* plants are tabulated in **Table 2**.

Other Pharmacological Activities

Cinnamomum plants have also shown an array of other biological activities. (Nyadjeu et al., 2011) reported that *C. verum* extracts decreased arterial blood pressure in rats with normal arterial hypertension and various models of hypertensive rats (salt-loaded and spontaneously) (Nyadjeu et al., 2011). In another study, (Wansi et al., 2007) reported that *C. verum* extracts showed similar effects in arterial blood pressure of normotensive rats and salt-loaded hypertensive rats. Moreover, they showed that *C. verum* had a vasorelaxant action on the thoracic aortic ring segments, which suggests that *C. verum* might inhibit

extracellular calcium through L-type voltage-sensitive channels (Wansi et al., 2007).

The antiparasitic effects of EOs from bark and leaves of *C. verum* were investigated by (Samarasekera et al., 2005) against *Anopheles tessellates, Culex quinquefasciatus*, and *Aedes aegypti*. These oils showed knock-down and mortality against *A. tessellatus* (LD_{50} = 0.33 μg/ml) and *C. quinquefasciatus* (LD_{50} = 0.66 μg/ml). (Yang et al., 2005) showed fewer effect of *C. verum* bark EO against *Pediculus humanus capitis* (eggs, adult females of human head louse) than either phenothrin or pyrethrum using direct contact bioassay (Yang et al., 2005).

Collagen synthesis was stimulated in human dermal fibroblasts by *C. verum* extracts (Takasao et al., 2012). *C. verum* extract enhanced both mRNA and protein expression levels of type I collagen without cytotoxicity, and cinnamaldehyde was the most active component stimulating the expression of collagen, suggesting that *C. verum* extracts might be useful in skin anti-aging treatments (Takasao et al., 2012). Moreover, *C. verum* extracts inhibited osteoclastogenesis (Tsuji-Naito, 2008). At concentrations of 12.5–50 μg/ml, *C. verum* inhibited osteoclast-like cell formation in a dose-dependent manner without affecting cell viability. This finding suggests its potential use in the treatment of osteopenia diseases (Tsuji-Naito, 2008). In addition, *C. verum* exhibited *in vivo* anti-secretagogue and anti-gastric ulcer effects (Alqasoumi, 2012). In pylorus-ligated rats, *C. verum* extract pre-treatment reduced the basal gastric acid secretion and inhibited gastric hemorrhagic lesions (Alqasoumi, 2012). Furthermore, *C. verum* extracts at 100 and 200 mg/b. w. effectively diminished the extent of diarrhea (71.7 and 80.4%, respectively) in test animals (RAO, 2012).

In another research performed in two rat models, the evaluation of anti-nociceptive effects of *C. verum* and selected plants showed that *C. verum* produced a dose-dependent analgesic protective effect against thermal stimuli. Moreover, *C. verum* enhanced an anti-inflammatory activity against chronic inflammation of cotton pellet granuloma (Atta and Alkofahi, 1998; RAO, 2012). *C. verum*has also demonstrated wound healing properties (Kamath et al., 2003; Farahpour and Habibi, 2012). *C. verum* (0.01, 0.05, and 0.1 g/b. w. for 28 days) displayed hepatoprotective effects in a study where the liver injury was induced in rats by CCl_4 (carbon tetrachloride) (Eidi et al., 2012). Other pharmacological properties of *Cinnamomum* plants are summarized in **Table 2**.

CLINICAL TRIALS RELATED TO EFFICACY OF BIOACTIVE COMPOUNDS DERIVED FROM *CINNAMOMUM*

Type 2 Diabetes Mellitus, Obesity and Metabolic Syndrome

Cinnamon consumption was associated with reduction in the levels of fasting plasma glucose (FPG), total cholesterol (TC), triglyceride levels (TG), LDL cholesterol and hemoglobin A1c (HbA1c). In one study, cinnamon consumption resulted in significantly increased FPG levels and HbA1c (Blevins et al., 2007) or no significant change in HDL cholesterol levels. However, the most preferred and effective doses with fewer side effects are still not clear. Doses applied in randomized clinical trials showed conflicting results as consumption of 1 g/day (Khan et al., 2003; Blevins et al., 2007; Crawford, 2009), 1.5 g/day (Vanschoonbeek et al., 2006; Radhia et al., 2010), 2 g/day (Akilen et al., 2010), 3 g/day (Khan et al., 2003; Mang et al., 2006; Vafa et al., 2012), or 5 g/day (Gutierrez et al., 2016), 6 g/day (Khan et al., 2003) showed different effects in glycemic and lipid parameters. FPG and HbA1c are commonly used parameters for diabetes diagnosis. HbA1c values of more than 6.5% can be related to diabetes. Vafa et al. showed FPG and HbA1c at baseline modestly elevated (7.02 mmol/L to 8 mmol/L) and 6.9–8.0%, respectively (Vafa et al., 2012). Both the studies by Akilen et al. and Crowfrod reported a drop of 0.36 and 0.83% of HbA1c values at low dose cinnamon supplementation which were safe and well tolerated for 3 months in patients using simultaneous hypoglycemic medications (Crawford, 2009; Akilen et al., 2010). Mang et al. observed that aqueous extract of cassia cinnamon significantly reduced glucose levels like 10.3% in the cinnamon group and 3.4% in the placebo group, however, no considerable difference in HbA1c and cholesterol (LDL, HDL, TC) levels were observed (Mang et al., 2006). Suppapitiporn et al. observed no significant differences in cinnamon and placebo group for FPG and lipid profiles but HbA1c level decreased in both groups by 0.38 and 0.19% respectively (Suppapitiporn and Kanpaksi, 2006).

Khan et al. reported that intake of 1, 3, or 6 g of cinnamon reduced fasting serum glucose by 18–29%, LDL by 7–27%, triacylglycerol by 23–30%, and total cholesterol by 12 26% after 40 days treatment. Nevertheless, they did not investigate the HbA1c value (Khan et al., 2003). One study showed that, consumption of *Cinnamomum cassia* powder 1.5 g/day for 6 weeks, did not improve plasma glucose levels, insulin, and cholesterol levels and no reduction in HbA1c level was noted (Vanschoonbeek et al., 2006). Only one trial by Blevins et al. observed significant increases in HbA1c and FPG levels (Blevins et al., 2007). In healthy, sedentary and obese women with *Cassia* supplementation a statistically significant reduction in glucose level was noted suggesting that the bark of *Cassia*can improve glucose tolerance. However, this study did not mention the acute dose of *Cassia* to maintain insulin resistance or sensitivity (Gutierrez et al., 2016). Some studies proposed that cinnamon also improved lipid profiles in clinical trials. Vafa et al. showed that in type 2 diabetes treated with cinnamon increased LDL levels but decreased TC, insulin and triglyceride levels with the improved glycemic index (Vafa et al., 2012). In addition, intercellular adhesion molecule-1 (ICAM-1) levels are increased in serum associated with increasing type-2 diabetes. Azimi et al. studied that consumption of *Cinnamomum verum* extract for 8 weeks decreased serum ICAM-1 level in patients with type-2 diabetes (Azimi et al., 2016).

26 clinical trial studies on cinnamon are present on Clinical Trials Govt. Database, among them most of the studies are under process and 14 studies are completed. Clinical trial numbers NCT03219411 and NCT01301521 showed effects of cinnamon supplementation in pre-diabetic patients. Clinical trials

NCT03711682 and NCT00237640 observed plasma glucose and lipid levels reduction mediated by cinnamon in type 2 diabetic patients and in noninsulin dependent type 2 diabetes mellitus patients respectively. NCT01302743 trial demonstrated the application of water-soluble cinnamon bark extract and metformin for the treatment of type 2 diabetes mellitus patients. **Table 3** displayed the clinical studies on Cinnamon plants in relation to diabetes.

Neurodegenerative Disorders

Neurodegenerative disorders (ND) include disorders like Alzheimer's disease, amyotrophic lateral sclerosis, Parkinson's disease, Huntington's disease, motor neuron disorder, and frontotemporal dementia that result from slow progressive and unalterable drop of certain areas of the nervous system, leading to disruption in nervous system working or death (Nussbaum et al., 2017).

Various *Cinnamomum* species displayed efficacy in the management of neurodegenerative diseases. Several *in vitro* studies are present for cinnamon that can regulate factors that trigger neurodegenerative diseases. Cinnamon extract inhibited Tau aggregation *in vitro* attenuating Alzheimer's diseases (Peterson et al., 2009). *C. cassia* bark extracted in ethanol demonstrated *in vitro* efficacy against Huntington disease Kaur and Shri (2018). Therefore, cinnamon is necessary to put into clinical trials that develop drugs for neurodegenerative disorders. One clinical trial (NCT03225144) for patients with motor neuron disorder, frontotemporal dementia, or related adult-onset neurodegenerative disorder is ongoing involving 200 participants (**Table 3**).

Polycystic Ovary Syndrome: A Possible Control on Its Metabolic Parameters

Polycystic ovary syndrome (PCOS) is caused by an associated endocrine dysfunction and is associated with increased risk of developing insulin resistance, type 2 diabetes, high blood pressure, hypercholesteromy and heart disease.

Several clinical trials reported conflicts in results for cinnamon efficiency on the improvement of BMI, body weight, oxidative stress, and fertility (Hajimonfarednejad et al., 2018a; Borzoei et al., 2018b; Khan and Begum, 2019). Consumption of daily 1.5 g cinnamon did not show any significant effect on BMI and body weight but improved glucose balance in patients with PCOS (Hajimonfarednejad et al., 2018a). However, Borzoei et al. decreased BMI and improved glucose balance treated with the same concentration as applied by Hajimonfarednejad et al. (Hajimonfarednejad et al., 2018a; Borzoei et al., 2018b). Oral supplementation of cinnamon also showed weight loss. This study further exhibited decreased BMI in comparison to the placebo group in PCOS patients (Talaat and Ammar, 2018; Parseh et al., 2019). In contrast to the report by Hajimonfarednejad et al. and Kort and Lobo observed that oral cinnamon consumption did not show any effect on serum glucose balance in PCOS patients (Kort and Lobo, 2014a; Hajimonfarednejad et al., 2018a). This study also supported by Parseh et al., who also did not report any changes in glucose homeostasis (Parseh et al., 2019). All of the studies discussed here showed an effective dose of cinnamon as 1.5 g per day, three times after meal for 1.5–6 months except Talaat and Ammar reported effective dose of 336 mg cinnamon extract per day whereas Wiweko and Susanto (2017) treated with 200 mg of *Cinnamomum burmanii* and *Lagerstroemia speciosa* combination extract (Talaat and Ammar, 2018).

Serum LDL-C, TG and TC levels were also found to be improved in PCOS patients in comparison to placebo (Hajimonfarednejad et al., 2018a; Borzoei et al., 2018b). However, HDL-C level did not show any significant improvement (Borzoei et al., 2018b). Khan and Begum observed no changes in insulin resistance and did not found any significant improvement in patients' life in comparison with metformin treatment as a control (Khan and Begum, 2019).

Herbal medicine combination extract of *Glycyrrhiza glabra, Paeonia lactiflora, Cinnamomum verum* and *Hypericum perforatum* (supplemented with 1.5 g tablet per day for 3 months) with lifestyle intervention positively improved menstrual regulation and reduction in oligomenorrhoea of 32.9% in patients in comparison with only lifestyle intervention in overweight women with PCOS (Arentz et al., 2017).

Oxidative stress is one of the main causes for increasing lipogenes, BMI in PCOS due to molecular damage, and reduction of serum antioxidants. Borzoei et al. demonstrated that cinnamon extract has antioxidant activity that can improve oxidative stress in women with PCOS (Borzoei et al., 2018a). **Table 3** summarized the clinical studies on cinnamon plants in relation to PCOS.

TOXICOLOGICAL SAFETY AND ADVERSE EFFECTS OF NATURAL DERIVATIVES OF *CINNAMOMUM* SPECIES

Besides the numerous health benefits, all phyto-therapeutics are not always safe and might result in adverse effects such as allergic dermatitis, the toxicity of organs and interactions with foods and pharmaceuticals (Calixto, 2000). The usual dose for dietary supplements has been suggested to be between 1 and 4 g per day (NIHU, 2015). The usual doses for the administration of cinnamon oil, which is stronger, vary between 50 and 200 mg per day. For doses up to 6 g per day, no adverse reactions were reported (Yun et al., 2018). The common use of cinnamon in food as a spice, food additives and flavoring agent would suggest that it is likely to be safe (Gowder, 2014). However, when consumed in excess, cinnamon can cause respiratory distress, increase pulse rate and increase the sweating process, followed by depressive and drowsy states. This may aggravate the symptoms of rosacea and may increase the risk of developing oral cancer. Coumarin, naturally found in cinnamon, can have a negative influence on the liver, so people with liver disorders should avoid excessive consumption (Organization, 2001).

Cinnamon extract at different doses didn't produce any toxicity or mortality on rats, as well as no adverse effect was observed (Ahmad et al., 2013) though *trans*-cinnamaldehyde and coumarins are toxic components of cinnamon (Woehrlin et al., 2010; Zhang

et al., 2010). High levels of coumarin and cinnamaldehyde might be correlated to liver damage (Deng, 2012), risk of cancer (Abraham et al., 2010), mouth sores (Vivas and Migliari, 2015), low blood sugar (Adisakwattana et al., 2011; Deng, 2012) breathing problems and interaction with certain medications (Abraham et al., 2010). Therefore, the long-term use of a high amount of cinnamon should be continuously monitored. The tolerable daily intake for coumarin (0.1 mg/b. w.) is to be regarded as safe in terms of daily cinnamon intake without the risk of adverse effects (Abraham et al., 2010). When used in large quantities *Cinnamomum* may interact with certain drugs, which could damage the liver.

Used externally, the cinnamon essential oil can produce skin redness, irritation and burning sensation in the *epidermis* (Markman, 2002). In addition, negative interactions with the drugs such as statins, acetaminophen, amiodarone (used to treat heart conditions), carbamazepine (given in the treatment of seizures), medicines for treating fungal infections, methotrexate (used in antitumor treatments) and methyldopa (used in hypertension) may also occur.

Because cinnamon can reduce the concentration of blood sugar, consumed in large quantities, it can interact with diabetes medicines, leading to a very low level of sugar. It is also possible to interfere negatively with tetracycline. Noteworthy, the safety of cinnamon is dependent on supplier quality assurance (SQA), good manufacturing practice (GMP) and good agricultural practice (GAP). It is necessary to control the cultivation, harvesting, plant identification, contamination, adulteration, preparation, packaging, transportation, storage etc. In order to guarantee the safety of the cinnamon products, it is required to assess the quality control of identity/authenticity and purity, stability and shelf life, toxicity physical/chemical/biological/ microbial properties and finally standardization of the plant material as well as the products (Kumari and Kotecha, 2016).

DISCUSSION

One of the strengths of this updated review is that the pharmacological effects highlighted in preclinical *in vitro* studies and in vitvo models could be translated into recent clinical trials in human subjects at well-defined doses, providing strong scientific evidence-based support for therapeutic effects. ethnopharmacological features of cinamomum species.

In addition, current toxicological data show that unwanted side effects may occur at higher doses of cinnamon than shown in pharmacological studies.

Another strength of this comprehensive review is the summarized presentation of the pharmacological mechanisms and molecular targets of action resulting from the meta-analyzes included in the study in order to open new clinical pharmacotherapeutic perspectives.

Starting from traditional uses, pharmacognostic research on *Cinnamomum* plants have identified chemical compounds with biological activities. Three major components found in cinnamon oil and powder: are cinnamaldehyde, acetate, and cinnamyl alcohol, give it beneficial properties. Also, cinnamon is a good source of iron, calcium, manganese and dietary fiber (Vallverdú-Queralt et al., 2014).

Plant organic extracts are a rich source of antimicrobial agents and methanol extracts are known for their antimicrobial properties. Indeed, organic solvents have a good ability to solubilize the active components (de Boer et al., 2005) and their use does not influence the bioactivity of these components (Goyal et al., 2009). (Thongson et al., 2004) also suggested that organic solvents are better solvents of antimicrobial substances. Therefore, a number of preclinical experimental *s*tudies showed the antibacterial effects of *Cinnamomum* plants. Secondary metabolites of Cinnamon plants have the ability to adhere to the microbial cell surface by crossing the lipid layer of the cytoplasmic wall, thus accumulating in the bacterial cell wall. Therefore, phytochemicals alter the structure of the membrane and increase its permeability, causing leakage of vital intracellular metabolites and, finally, cell death (Rhayour, 2003; Wu et al., 2009).

The bacterial cytoplasmic membrane plays a role in selective permeability by ensuring the crossing of H^+ and K ions$^+$. The maintenance and regulation of this barrier are provided by the structural, chemical composition of the cell wall. Increased ion leakage means a disruption of the permeability barrier. Cell metabolism can be influenced by changes in the structural integrity of the cell membrane that, in turn, can lead to the death of cells. (Cox et al., 2001).

Several preclinical experimental studies have been developed to highlight the antidiabetic effects of natural molecules from *Cinnamomum* species. Current conventional therapies used in the treatment of diabetes have many limitations, such as short- and long-term undesirable effects and high rates of failure (Sharifi-Rad et al., 2020a). Therefore, it is necessary to develop more effective drugs to treat diabetes. Presently, complementary herbal remedies are expected to have hypoglycemic properties similar to those of conventional medications without troublesome side effects (Sharifi-Rad et al., 2020b). Traditional herbs and spices can also delay the onset of diabetic complications, control blood sugar levels and correct metabolic abnormalities. The *in vitro* methods are essentially based on the inhibition of enzymes involved in the carbohydrate catabolism and therefore sugar absorption. However, the determination of the *in vivo* antidiabetic activity requires the development of approaches such as oral glucose tolerance test, streptozotocin (SZT)-induced diabetes and alloxan-induced animal models.

The potential mechanisms of antidiabetic effects of Cinnamomum species were highlighted by **r**ecent studies. These have shown that secondary plant metabolites, such as terpenoids and flavonoids, have a significant hypoglycemic effect (Marles and Farnsworth, 1995). Terpenoids stimulate insulin secretion from pancreatic β-cells (Marles and Farnsworth, 1995) whereas cinnamaldehyde has a significantly anti-hyperglycemic effect (Subash Babu et al., 2007).

The antioxidant properties of *Cinnamomum* plants have extensively reported. Polar extracts of the leaves, fruits and seeds, as well as several pure compounds, exhibited relevant activities in a variety of antioxidant assays when compared to positive controls. Cinnamon extracts and its phenolic compounds

showed important free radical scavenging properties by the modulation of key enzymes implicated in oxidative stress or by modulation of oxidative pathways that influence the maintaining of redox homeostasis. Cinnamon extracts enhanced ferric reducing antioxidant power (FRAP) and plasma thiol (P-SH), and decreased MDA levels. In addition, they also increased antioxidant enzyme properties such as SOD and catalase (Moselhy and Ali, 2009; Roussel et al., 2009). Our study also showed that Cinnamomum derivatives have a good anti-inflammatory properties.

The antitumor effects of *Cinnamomum* species have been reported by several studies (Koppikar et al., 2010; Kwon et al., 2010; Wondrak et al., 2010; Daker et al., 2013). These antineoplastic activities were tested *in vitro* on several types of human cancer cell lines. These studies highlighted the next possible anticancer mechanisms of *Cinnamomum* plants: 1) inhibition of tumor cells growth (Koppikar et al., 2010), 2) the cinnamon extract is a potent activator of the transcription factor NRF2 (nuclear factor erythroid 2-related factor 2) orchestrated antioxidant response in human cells (Wondrak et al., 2010), 3) cinnamaldehyde involves apoptosis mediated by the increase of p53 and APO-19 (Fas/CD95) protein signaling pathways (Ng and Wu, 2011), 4) DNA (deoxyribonucleic acid) damage (Ng and Wu, 2011), v)apoptosis mediated by the tyrosinase inhibition (Chen et al., 2007; Wang et al., 2011), 6) reducing the mitochondrial transmembrane potential, increasing the ratio of cytochrome C concentration and subsequently activated caspase-9/caspase-3 (Lin et al., 2009).

Recent studies showed neuroprotective effects of *Cinnamomum* plants and their derivatives. The aqueous extract of *C. verum* reduced tau aggregation and filament formation, the markers of Alzheimer's disease (Peterson et al., 2009). From the brains of patients diagnosed with Alzheimer's disease, the *C. verum* extract produced the complete disassembly of recombinant tau filaments and caused important alteration of the histology of paired helical filaments isolated, even though it was not deleterious to the normal cellular function of tau. (Peterson et al., 2009). Specifically, the proanthocyanidin, a chemical constituent isolated from the *C. verum* extract was observed to be mainly responsible for this inhibitory activity (Peterson et al., 2009).

Recent clinical studies have found that complementary herbal treatments with cinnamon regulate the frequency of menstrual cycles and may reduce insulin resistance in women with polycystic ovaries.

Regarding the toxicity data, some clinical studies reported that the most common adverse events after cinnamon consumption were gastrointestinal problems in patients with diabetes (Altschuler et al., 2007; Crawford, 2009), *Helicobacter* infection (Nir et al., 2000), polycystic ovarian syndrome (Kort and Lobo, 2014b) and seasonal allergies (Walanj et al., 2014). Dermatitis (Calnan, 1976; Ackermann et al., 2009; Isaac-Renton et al., 2015) and steatites (Miller et al., 1992; Endo and Rees, 2007) were also reported in some case reports. A systematic review of clinical trials and case reports/series on side effects associated with the use of cinnamon in humans indicated that no important difference obtained between cinnamon treated and control group in most cases (Food and Administration, 2005; Hajimonfarednejad et al., 2018b).

Further efforts should be made to investigate future applications of standardized *Cinnamomum* plants using well-designed research.

OVERALL CONCLUSIONS

Cinnamomum plants, its extracts and chemical constituents have several activities promoting human health. Antibacterial, antidiabetic, antioxidant, anti-inflammatory, antitumor and neuroprotective activities are the most studied biological properties of *Cinnamomum* plants. Different from conventional therapeutic medicines, *Cinnamomum* species can be daily consumed in our diet without harmful effects and maybe used as a disease-preventive agent.

In general, chemical constituents of *Cinnamomum* plants such as cinnamon, cinnamaldehyde, cinnamophilin and others, have both direct and indirect activities, *i.e.* antioxidant and antibacterial activities occur by direct action on oxidant species or bacterial, whereas the antidiabetic, anticancer and anti-inflammatory activities occur indirectly via some yet undefined receptor-mediated mechanisms. In this present review, we have retrieved and summarized the wide applications and recent literature on the phytochemistry, bioactivity and pre-clinical and clinical investigations performed on many species of the genus. Besides, a detailed account on their toxicological considerations also indicate their safety and efficacy for human consumption. However, since a plethora of reports exist on the plant species, details on ethnobotany, biotechnological interventions and detailing structure-activity studies are beyond the scope and coverage of the present attempt.

Botanical research advances can improve the obtaining of *Cinnamomum* plants with the best phytochemical compounds. Moreover, the antimicrobial effects of *Cinnamomum* spp. can be potentiated in the food industry as the development of green foods.

AUTHOR CONTRIBUTIONS

JS-R, AD, and DC conceptualization. MM, AD, NK, SS, NE, and BH validation investigation. NC, CS, AB, and SV resources. BS, MM, AD, EV, and FL. VL, TG, AA, and CC. data curation. JS-R, AD, FL, BS, VL, CC, and DC review and editing. DC supervision. All authors: writing. All authors read and approved the final version and contributed equally to the article.

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