Review Article

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Sources, extraction and biological activities of cinnamaldehyde

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Abstract

Cinnamaldehyde is the prevalent bioactive part of cinnamon essential oil which is liable for its regular scent and can be gotten from the bark, leaves, and twigs of various *Cinnamomum* species. Cinnamaldehyde is known to be generally considered non-toxic due to its high tolerance in animals and humans. Various extraction methods have been used for extracting cinnamaldehyde and different phytochemicals from plants. The methods generally adopted for cinnamaldehyde extraction are hydro distillation, supercritical carbon dioxide extraction, ultrasound-assisted extraction, microwave-assisted hydro distillation, and water steam extraction. Cinnamaldehyde has been documented to have different useful properties against disease conditions as a result of oxidative stress, inflammation, loss of neurons, hyperglycemia, and malignant growth. Likewise, cinnamaldehyde has been recorded to possess strong antimicrobial activity against a wide range of pathogenic and food waste microorganisms. The mechanism through which cinnamaldehyde exerts these effects have been associated with the prevention of reactive oxygen species and reactive nitrogen species generation, free radical scavenging activity, inhibiting inflammatory cytokines, and disruption of the cell membrane of microorganisms. This article gives a thorough report of the sources, extraction techniques, validated therapeutic potentials and mechanisms of cinnamaldehyde. It likewise features other applications of cinnamaldehyde in agriculture, food, and other industries.

Keywords: Antimicroial, Anticancer, Antidiabetes, Cinnamon, Cinnamaldehyde.

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Introduction

The use of medicinal plants by the traditional system for treatment and management of diseases continues to be the main stay in low-come countries due to their natural source, safety, affordability, and availability (1, 2). Unpleasant side effects and the cost of available drugs are underlying reasons, among others, which have triggered a renewed interest in natural sources for the development of therapeutic agents. Extracts, essential oils and other plant derivatives from various parts of plants are different forms in which these plants are used for their therapeutic potentials. These pharmacological effects of medicinal plants, such as antimalarial, anticancer, antifungal, antiviral and antidiabetes, among others, are because of the inherent secondary metabolites known as phytochemicals (3). The most common phytochemicals such as flavonoids, phenols, sterols, tocopherols, and organic acids possess appreciable health benefits and other applications in the development of pharmacotherapeutic and nutraceutical foods. This review article lays emphasis on the therapeutic potential of cinnamaldehyde in the management of commonly occurring diseases and other applications.

Cinnamaldehyde also known as cinnamic aldehyde is an α, β-unsaturated aldehyde derived

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Table 1. General physicochemical properties of cinnamalydehyde.

Properties	Description
IUPAC name	(E)-3-phenylprop-2-enal
Chemical formula	C9H8O
Molecular mass	132.16 g/mol
Solubility in water	Slightly at about 1.1g/L at 20oC
Colour	Yellow to greenish yellow
Density	1.05 g/mL at 25oC
Boiling point	248oC (478oF)
Melting point	-7.5oC (18oF)
Bisulfide solubility	100%
Purity	>98%

from cinnamon trees and other species of the genus Cinnamomum, it is responsible for their characteristic natural flavour and fragrance. Cinnamaldehyde is a clear yellow to greenish yellow liquid compound with a pungent spicy note and accounts for 85% of the constituentsof essential oil of cinnamon bark. Cinnamaldehyde is well-tolerated in both humans and animals and generally considered as a safe bioactive. Cinnamaldehyde was first isolated from cinnamon essential oil in 1834 and was first synthesized in the laboratory in 1856 by Chiozza (4). Different methods for laboratory synthesis of cinnamaldehyde are currently available but the use of steam distillation of the oil from cinnamon bark is considered most economical (5). It can be synthesized from cinnamyl alcohol, aldol condensation of benzaldehyde and acetaldehyde etc. the general physicochemical properties of cinnamaldehyde is discussed in table 1.

Studies have shown that cinnamaldehyde possess the ability to eliminate natural or chemical toxins like ochratoxins A, as well as improve general human wellbeing (6, 7). The bioactivities of cinnamaldehyde have been duly documented in literatures (8-11) and have also been reported to have other applications in agriculture as a preservative (12). Due to the bioactivities and other applications, it is of significant worth to rationally put together research findings related to the therapeutic potentials and agricultural importance of cinnamaldehyde in other to expound its importance to human health and food security. This review will also discuss the mechanisms involved in the functionality of cinnamaldehyde preventing numerous lifestyle related health conditions.

Sources of Cinnamaldehyde

Cinnamaldehyde ($C_6H_5CH=CHCHO$), the major organic compound of cinnamon essential oil (13). Cinnamaldehyde, which is an important flavour component of cinnamon, is obtained from the *Cinnamomum genus*. They include *Cinnamomun zeylanicum* L (Cinnamon) (13), *Cinnamomum tamala*, *Cinnamomum pauciflorum* (14), *Cinnamomum ceylanicum* (Ceylon) which is the most appraised source, *C. cassia* (cassia) and *C. burmannii* (cassia vera) which are frequently used as cheaper alternatives (15). Cinnamaldehyde can be extracted from different parts of the plants including the bark, leaves and twigs (16, 17).

Extraction and Purification of cinnamadehyde

The extraction and isolation cinnamaldehyde have been done in various ways since time past. This review is going to highlight some ways cinnamaldehyde is being isolated and purified as reported by several authors. Figure 1 gives a glance of the different extraction methods used for cinnamaldehyde extraction.

High Performance Counter-Current Chromatography

In this process of isolation of cinnamaldehyde, the cinnamaldehyde will be enriched by Counter-Current Chromatography (CCC) with reversed phase mode using n-hexane-ethyl acetate-methanol-water (1:1:1:1, v/v/v/v) as the solvent system. Counter-current chromatography (ccc) is

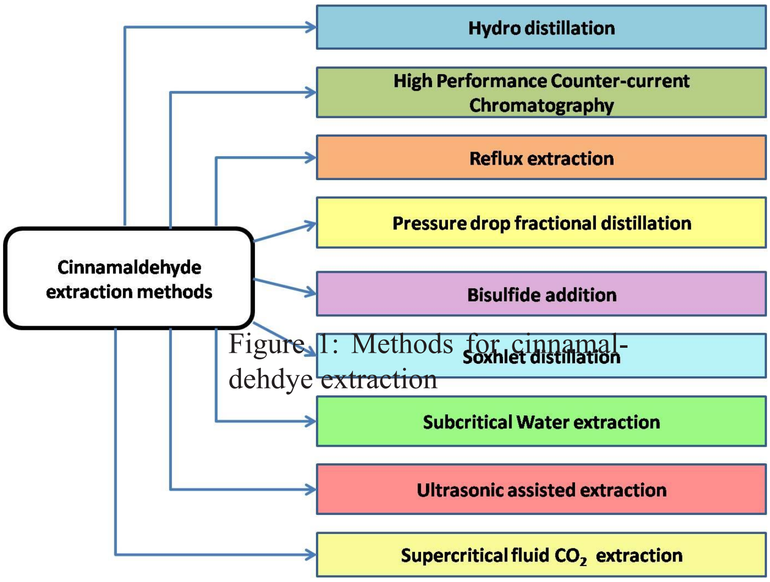

Figure 1. Methods for cinnamaldehdye extraction.

Figure 1: Methods for cinnamal-dehdye extraction

one of the liquid-liquid separation methods with many technical merits. Examples include ability to take less time and lower volume of solution selective and it gains higher recoveries. Fan *et al.*, (18) reportedly used the high-performance counter-current chromatography method to extract cinnamaldehyde from cinnamon bark.

Pressure Drop Fractional distillation

Isolation of cinnamaldehyde can also be done using the pressure drop fractionation as reported by Moreta *et al.*, (19). In the separation of cinnamaldehyde from cinnamon oil using fractional distillation, the use of pressure reduction is intended so that cinnamaldehyde can evaporate faster than regular boiling points. The pressure used in this process is usually around 29.8-30.1 mmHg and temperature 30-300 °C.

Bisulfite addition method

Bisulfite addition method is another method used to extract and isolated cinnamaldehyde. It is carriedout by reacting cinnamon oil to the saturated sodium bisulfite solution with a ratio of 1:1. The precipitate formed was further neutralizedwith 10% HCl solution. Furthermore, cinnamaldehyde will be extracted from the solution using petroleum ether twice and washed by sterile water. The petroleum ether extract will be applied in the evaporator (20).

Hydro Distillation (HD)

Hydro distillation is the most widely used method for cinnamaldehyde extraction, with advantages of simple process, lowcost, and absence of solvent residue, but it gives low yield at around 1-2 % (21, 22). Hydro distillation method has long been exploited in the extraction of essential oils and bioactive components of plant materials. Hydro distillation method of extraction can be carried out in three different ways: water distillation, water and steam distillation, and direct steam distillation (23). Three main physicochemical processes involved in hydro distillation are hydrodiffusion, hydrolysis, and decomposition by heat. Hot water and steam is generally considered as the basic media to break through plant matrix, thereby releasing bioactive compounds. The indirect cooling condenses the mixture of steam and bioactives and make separation of oil and bioactive components from the water to occur. Sodium sulphate is usually used for the dry of essential oils and oil-based bioactive compounds. Since hydro distillation is often conducted at temperature above boiling point of water, some volatile components, natural pigments, and heat-labile bioactive compounds may be lost (24).

Steps in extraction of cinnamaldehyde using this method is thus; weigh 10 gram of cinnamon bark powder and mix with 100 ml distilled water. The mixture is allowed for 2 days as soaking period. Extraction of essential oil from cinnamon bark powder then becomes easy after a soaking period. The mixture is then transferred into 2 litre distillation flask and heated on 50 °C. Distillate is condensed and collected into the beaker and then transferred into separating funnel. The mixture is then allowed to separate into oil and water phase. Oil will be settled on the water phase. Separation continues until there is no oil left in the water phase. Then store it in closed vessel at low temperature. Researchers have reportedly used this method to extract cinnamaldehyde (22, 25-29).

Water Steam Distillation

Water steam distillation is one of the types of hydro distillation methods used in extracting and isolating cinnamaldehyde. This was reported by Alsalim *et al*., (30) where they obtained cinnamaldehyde after 6 hours using steam distillation process following the process of Senhaji *et al* (31). In this method the cinnamon oil is usually transferred to a separation funnel, then about 5-10 ml of dichloromethane will be added to the separation funnel, shacked, and allowed to separate for 10 minutes, then dichloromethane will be drained off. This step is repeated once more. The above layer which contains the cinnamaldehyde will be dried by adding sodium sulfate until it is free flowing. The solution will then be transferred to a round bottom flask and the solid sodium sulphate was rinsed with a little more dichloromethane, then evaporated by rotary evaporator, cinnamaldehyde can then collected in dark container.

Subcritical Water Extraction (SWE)

Subcritical water extraction (SWE) is arising as a famous option for extraction of bioactive components. Water is used as extraction solvent at temperatures between 100 °C and 374 °C with a pressure (1-22.1 MPa) high enough to maintain the liquid state (32). Under subcritical conditions, the dielectric constant of water (directly related to its polarity) is reduced with increasing extraction temperature (for example, 80.4 at 20 °C to 27 at 250 °C), which consequently decreases the water polarity. As a result, water behaves like an organic solvent, thus allowing the extraction of different classes of compounds and selective extraction of target compounds (33). Subcritical water has been used to extract essential oil, polyphenols, and polysaccharide, *etc*. (34-41). Jayawardena and Smith (42) first extracted essential oils from cinnamon bark and leaves by SWE and confirmed that SWE is a practical method for cinnamon oil extraction. Subsequently, Eikani and colleagues (43) expanded the achievements of Jayawardena and Smith in terms of operating conditions and optimization procedure. They successfully optimized the SWE conditions of cinnamon bark oil and found that SWE is an effective method for the selective extraction of oxygenated components, such as E-cinnamaldehyde. Earlier studies (44) on the SWE of cinnamon oil also revealed that the extraction time of SWE is a sixth that of SD, and the yields of cinnamon oil and cinnamaldehyde are increased by 15.8% and 28.4%, respectively. In the mean time, it was found that the drawbacks of low mass transfer efficiency and uneven extraction became obvious alongside increase in loaded quantity and height of raw materials accumulation, particularly the material in the center of the extraction tank.

Ultrasound Subcritical Water Extraction (USWE)

To further improve the extraction yield, ultrasound, as an extraction strengthening technology, has been introduced into supercritical fluid to extract adlay oil, passion fruit seed oil and other bioactive components (45-47). These independent studies have proved that ultrasound can enhance supercritical fluid extraction. In recent years, the application of ultrasound in the SWE system is also developing gradually and has been found to effectively increase the extraction rate of SWE (48).

The apparatus for ultrasonic subcritical water extraction consists of SWE system, ultrasonic strengthening device and operating system, which has been reported in literature (49). The ultrasonic strengthening device mainly includes ultrasonic generator and transducer. The ultrasonic output power is between 0 and 250 W. The ultrasonic frequency can be adjusted between 15 kHz and 38 kHz. This operation is like SWE, except that USWE requires adjustment of the ultrasonic strengthening device. The powdered cinnamon bark will be extracted with distilled water at designed temperature, extraction time, pressure, and ultrasound conditions by the above USWE apparatus. After the extraction, the extract will be rapidly cooled down through cooling system to prevent degradation. Guo (50) also reported using this extraction method to extract and isolate cinnamaldehyde.

Soxhlet distillation

This method was initially designed by German chemist Franz Ritter Von Soxhlet in 1879 for lipid extraction from a solid material. These days, it is often utilized as a reference technique to evaluate extraction yield of lipid from plant materials. The principle of Soxhlet extraction is using a solvent vapour to dissolve oil-base compounds inside the plant sample housed in a thimble. The vapour is then condensed to separate the compounds of interest from the solvent. Although Soxhlet extraction is simple, inexpensive, and easy to operate, it requires a large amount of solvent, long extraction time, and leads to degradation of heat-labile bioactive compounds (51, 52). Masghati and Ghoreishi, (53) reported using soxhlet distillation method for cinnamaldehyde extraction.

Ultrasonic Assisted Extraction

The principle of ultrasonic assisted extraction is to use bubble cavitation created by ultrasound waves (20 kHz to 100 MHz) to rupture plant cell walls and intact plant materials, and thus, enhance the extraction efficiency. Cavitation is a phenomenon brought about by the passage of ultrasound wave through fluid medium creating alternative pressure and expansion pattern of bubbles. As the bubbles become too large to contain by its surface pressure, they breakdown bringing about massive shearing force and enormous amount of energy switching from kinetic energy of motion to completely heating of the bubble content. According to Suslick and Doktycz (54), the bubbles have temperature of about 5000 K, pressure of about 1000atm and heating and cooling rate above 1010 K/s. Based on this principle, only liquid and liquid-containing solid materials have cavitations effect. The Ultrasonic assisted extraction can effectively facilitate organic and inorganic compound leaching from plant matrix. Extraction efficiency is highly affected by moisture content of test sample, milling (processing) degree, particle size, and the nature of solvent used. Likewise, temperature, pressure, recurrence, and time of sonication are the key processing parameters for the activity of ultrasound. The ultrasonic assisted extraction can also be incorporated with other techniques to enhance the efficiency of a conventional system.

The advantages of ultrasonic assisted extraction include the ability to extract at lower temperatures due to the absence of external heat input, low solvent consumption, and reduction in extraction time. Ultrasound energy can likewise cause faster energy transfer, more effective mixing, lower thermal gradients and extraction temperature, specific extraction, and reduced equipment size. Among them, ultrasonic assisted extraction has the remarkable advantages of time and energy savings, higher extraction yield and better quality of essential oils owing to its cavitations, mechanical and thermal effects accelerating the extraction process (55, 56). Foudah *et al*., (57) reported using the ultrasonic assisted extraction method in extracting cinnamaldehyde from different species of cinnamon. Aryati *et al*., (58) also extract cinnamaldehyde from *Cinnamomum burmannii* barks.

Reflux Extraction

Reflux extraction (RE) is a traditional extraction method used to extract bioactive components from plant matrices. Althoughr, thermal degradation at high temperatures can occur over a long period of extraction. Additionally, longer extraction time requires more energy and extraction solvent (59). The procedure for reflux extraction according to the process by Ameer et al (60) is done using a water bath-equipped reflux extractor. All extraction experiments were executed utilizing the extraction parameters specified by CCD (Table 3). After extraction, the vessels will be cooled to room temperature and extracts filtered through Whatman filter paper No.41. Afterwards, the obtained extracts will be transferred to falcon tubes and stored at 4±1 °C (61). Ahmad *et al*., (62) and Zhou *et al*., (20) reported using reflux extraction method to extract cinnamaldehyde as well.

Supercritical fluid CO_2 extraction (SFE)

Supercritical fluids have high solubility of different compounds. Based on this principle, SFE has the advantages of high extraction efficiencies, mild extraction conditions avoiding the decomposition of targeted substances, easy solvent removal without toxic residues, and being environmental-friendly. In SFE, a particular gas is subjected to pressure and temperature past its critical point, above which characteristic gas and liquid phases do not exist. Supercritical fluid has liquid-like thickness and solvation power, and gas-like properties of diffusion, viscosity, and surface strain. These properties make it an excellent solvent to extract flavour and bioactive compounds from plant materials in a short time with higher yields at low temperature. As the pressure decreases, their salvation power increases (63). The most used solvent for SFE is CO_2, for it possesses the properties of being inert, odourless, inexpensive, non-toxic, non-flammable, and having a comparatively low supercritical pressure (74 bar) and temperature (32 °C). CO_2 is a non-polar molecule, so it is suitable for extracting non-polar compounds. This deficiency can be compensated by using modifiers such as ethanol (64, 65). The SFE is commonly operated in a temperature range of 30-60 °C and a pressure range of 8-40 MPa (52).

It is usually carried out using a supercritical CO_2 extraction apparatus SFE-2 (Applied Separations, America) for cinnamon essential oil extraction. About 20 g ground cinnamon sample will be weighed and then filled into the 50ml vessel. The oven temperature and the exit valve temperature will be set at 60 °C. The one-step static extraction will be performed at 30MPa for 2 hours, with no modifier. The extract will be collected directly without solvents and then sealed for preservation.

The SFE has many advantages over other extraction methods such as the absence of solvent residues and the rich top flavour notes of the extracts. Selective isolation of a single component from plant material can be achieved by using optimal process condition. Main factors influencing the extraction efficiency are temperature, pressure, particle size and moisture content of raw material, extraction time, gas flow rate, and solvent-to-raw material ratio (23). The only disadvantage of CO2 is its low polarity, which makes it unsuitable for the extraction of polar substances, which are common in pharmaceuticals and drug samples. This limitation has been successfully overcome using chemical modifier like dichloromethane (CH2Cl2). Usually, a small amount of modifier can significantly enhance the polarity of carbon dioxide (66). Despite the efficiency in extracting heat-labile bioactive compounds and the use of small quantity of solvent, the use of this method is limited due to the need for high capital and operating cost as a result of the high pressure required for the operation. Many reports have been written on its use to extract cinnamaldehyde from cinnamon species (29, 53, 67-70).

Microwave-assisted Hydrodistillation

In an attempt to take advantage of microwave heating with the conventional hydro distillation, microwave assisted hydro distillationwas then developed and used for the extraction of essential oils or extracts from some plants. With this technique, the plant material set in a Clevenger apparatus is heated inside a microwave oven for a brief timeframe to extract the essential oil where heat is produced by microwave energy. The sample reaches its boiling point quickly, resulting in an exceptionally short extraction or distillation time. After extraction, the oil will be dehydrated over anhydrous sodium sulfate to remove excess water, and then the concentrated oil will be weighed and stored in vial at 4 °C. Using the microwave distillation technique, it is possible to achieve distillation with the indigenous water of the fresh plant material (71). This method was also used by Jeyaratnam *et al*. (26). It was done thus Essential oil from Cinnamomum cassia (cinnamon) was extracted by using the microwave assisted hydro distillation method. Golmakani and Rezaei (72) also extracted cinnamaldehyde from the cinnamon bark through Microwave assisted hydro distillation. Hearrunyakij and Phutdhawong, (68) extracted cinnamaldehyde using this microwave assisted hydrodistialltion and compared it with hydro distillation and super critical fluid extraction method.

Validated Pharmacological Properties of Cinnamaldehyde

Cinnamaldehyde as a predominant component of essential oil extracted from cinnamon have been reported by various scientific investigations to possess therapeutic potentials. Different studies have been carried out to validate the traditional use of cinnamon oil for the management of diseases and infections and also to elucidate the mechanism by which cinnamaldehyde exerts its therapeutic activity. The general mechanism through which cinnamaldehyde exerts its therapeutic potential is through free radical scavenging, prevents the generation of reactive nitrogen species (RNS) or reactive oxygen species (ROS), elevation of cellular antioxidant defense. All these have been implicated in several disease conditions like diabetes, cancer, infectious diseases. Therefore, this section will summarize the various bioactivities of cinnamaldehyde against several infections, disease conditions and boosting general well-being.

Antimicrobial activity of cinnamaldehyde

The burden posed by infectious diseases continues to persist despite the different therapeutic agents available for managing infections due to continuous cases of antimicrobial resistance. Bacterial infections account for majority of infections that places both health and economic burden worldwide. Enteroccocus faecium, Pseudomonas aeruginosa, Klbesiella pneumonia, Acinetobacter baumannii, Staphylococcus aureus and Enterobacter species are the bacteria of greatest concern and most dangerous human pathogens (73). Cinnamaldehyde has been reported in various studies to possess antimicrobial activities against some food-borne and human pathogens. Due to the continuous multidrug resistance of these pathogens and prevalence of other less threatening and food borne pathogens, there is renewed interest in discovery and development of antibacterial agents from natural sources with low toxicity and affordability. Cinnamaldehyde has also received attention due to the therapeutic potentials folkloric medicine claim to possess. Several literatures have validated the traditional claims and reported the antibacterial activities of cinnamaldehyde against food-borne pathogens and human pathogens.

The antimicrobial activity of cinnamaldehyde in a study carried out by Shen et al., (74) against gram-positive Staphylococcus aureus and gram-negative *Escherichia coli* was observed to be through altering of bacterial cell morphology, disruption of membrane integrity and permeability. In an antivirulance study of cinnamaldehyde against *Staphylococcus aureus* and *Enterococcus faecalis* multidrug resistant strains, it was observed that cinnamaldehyde inhibited the heamolytic activity of the bacteria in human red blood cells. Additionally, the *in vivo* study in *Galleria mellonella* larvae model showed that cinnamaldehyde possess the ability to decrease bacterial virulence and survival rate without causing any phenotypic change (75). Cinnamaldehyde exhibit potent antibacterial activity against various strains of bacteria such as *Streptococcus pyogenes*, *Pseudomonas aeruginosa*, *Staphylococcus epidermidis*, *Staphylococcus pseudintermedius*, *Proteus mirabilis*, *Septococcus mutans* and *Salmonella Typhimurium*, *Aeromonas hydrophila*. Cinnamaldehyde exhibit antimicrobial activity against bacteria by disrupting cell membrane leading to leakage of intracellular components leading eventual death of the cells, inhibiting genes responsible for some proteins and inhibiting the production of biofilms in biofilm producing bacteria. He *et al*., (76) reported cinnamaldehyde inhibition of biofilm formation by modulating hydrophobicity, aggregation, acid tolerance and acid production. It also inhibited virulent gene expression.

Antifungal potential of cinnamaldehyde in food plants and cash crops has also been explored and reported by numerous studies. Cinnamaldehyde appears to exhibit its antifungal abilities through inhibiting the growth of fungal spores, inhibiting the biosynthesis of aflatoxin in aflatoxin producing fungi Aspergillus niger. The aflatoxin biosynthesis is inhibited by altering the normal functions of GPCRs and Oxyipins, biosynthesis of cell wall, as well as redox balance. At a concentration of 0.2 µL/mL Mean inhibitory concentration (MIC) that is, 50% of inhibition was observed in Alternaria alternate (77). Some of the fungi that cinnamaldehyde has been reported to possess antifungal activity against include *Aspergillus niger*, *Aspergillus ochraceus*, *Alternaria alternata*, *Candida alicans*, *Malassezia pachydermatis*, *Phytophthora capsici*, *Aspergillus flavus*.

Table 2. Summary of mechanism of cinnamaldehyde activities.

Bioactivities	Mechanism	Ref
Antibacterial	Damage bacterial cell morphology	74, 76,79,
	Cell membrane integrity and cell permeability damage (Cell lysis)	80-82
	Inhibit biofilm formation	
	Inhibit Salmonella pathogenicity island 1 (SPI-1)	
Antifungal	Inhibits biosynthesis and degrades mycotoxins	7,77,83-86
	Destruction of mitochondria.	
	plasma membrane and loss of cell wall integrity	
	Pertubation of fatty acid, polysaccharide and leucine metabolism	
Antiviral	Stimulation of TLR7 pathway	87
	Activation and increased expression of IRAK-4	
Antioxidant	Inhibits Aryl hydrocarbon receptor (AHR) activation	88,89
	Activates NRF2/HO1 pathways	
	Up-regulation of Hmox1	
	Inhibits MAPK signaling pathway	
Antidiabetic	Regulates PTP-1B and a-amylase	90-92
	Activates AMPK	
	Upregulates IRS1/PI3K/AKT2 pathway	
	reduced AGE/RAGE interaction	
Anti-inflammation	Regulation of Janus kinase/Signal transducer and activator of transcription (Jak/Stat) pathway	93,94
	Blocks NF-κB pathway	
Anticancer	Inhibition of Wnt/β-catenin pathway	95,96
	Inhibit proliferation related protein expression eg. p62	
	Induction of Beclin-1, ATG5 and LC3B expression	
Anti-neurodegenerative	Inhibits tau aggregation	97-99
	Activation of SIRT1-PGC1α-PPARγ pathway	
	Reduction of GSK-3β protein level	

Cinnamaldehyde has the ability to limit viral infection and replication against enteric viruses. Enteric viruses are viruses that are mainly transmitted through the faecal-oral route, either based on person to person contact or consumption of contaminated food or water. Cinnamaldehyde was observed to have virucidal activity against food-borne pathogens such as human norovirus and hepatitis A virus (78). The mechanisms through which cinnamaldehyde carries out its therapeutic functions are shown in table 2.

Antioxidant activity of cinnamaldehyde

Oxidative stress caused by the excessive production of reactive oxygen species and reactive nitrogen species (oxidants) in human body accounts for the pathogenesis of a number of diseases such as cancer, diabetes, Alzheimer's disease (100, 101). The mopping up of these oxidants appears to be a promising measure to reduce the level of oxidative stress. Secondary metabolites known as phytochemicals present in fruits and vegetables, as well as medicinal plants have been reported to scavenge these oxidants (102). Thus, playing an important role in the prevention and management of diseases linked with oxidative stress. Cinnamaldehyde, a potent phenylpropanoid predominant in cinnamon essential oil is majorly responsible for its free radical scavenging and antioxidant activity. The mechanism of action of cinnamaldehyde as an antioxidant agent could be due to up-regulation of antioxidant enzyme Hmox1, reduction in malondialdehyde accumulation and free radical-scavenging. *In vivo* study reported that cinnamaldehyde protected against lipid peroxidation in the brain and kidney of rats (103). All these reports points cinnamaldehyde as a possible therapeutic agent against oxidative stress related disease conditions.

Anti-inflammatory activity of cinnamaldehyde

The body has a natural mechanism of defense known as inflammation. This is the process the immune system adopts in recognizing and removing harmful and/or foreign stimuli and initiates the process of healing. Inflammation can be named as acute or chronic relying upon the amount of time it requires to get to a serious state and how long the effects persevere.

Inflammation can be classified as acute or chronic depending on how long it takes to reach a severe state and how long the symptom persists (104). Acute inflammation is an important and constructive response by the immune system against tissue damage however delay in remediation may lead to metabolic related conditions like inflammatory bowel, arthritis and cancer. This occurs as a result of the movement of neutrophils and macrophages into infected tissues from the blood stream (105). Chronic inflammation is a prolong reaction to biological, chemical or physical stimuli defined by continued deployment of mononuclear leukocytes alongside tissue injury as a result of continual inflammatory response (106). The development and progression of about 25% of cancers have closely been linked to chronic inflammation (107). The shift from synthetic to natural products for managing diseases including diseases associated with inflammation has led to the exploitation of cinnamaldehyde in the bid to develop novel drugs from plants with low toxicity and anti-inflammatory response. Cinnamaldehyde inhibited the IL-8 secretion and expression helicobacter pylori induced gastric inflammation. Additionally, cinnamaldehyde optimally inhibited inflammatory cell infiltration induced by lipopolysaccharide (LPS) (96).

Antidiabetic activity of cinnamaldehyde

Diabetes is a group of metabolic diseases characterized by high blood glucose level brought about by the alteration in the secretion and/or utilization of insulin. Diabetes is classified into type I and type II diabetes and cinnamaldehyde has been duly documented in literature to possess antidiabetic properties. Cinnamaldehyde exhibits its antihyperglycemic activity in diabetic animal models through increasing the uptake of glucose and enhanced glucogen biosynthesis in the liver, slowing the rate of gastric emptying, pancreatic islets dysfunction restoration and improved diabetic renal and brain disorders. All these effects are achieved by cinnamaldehyde through its action on different signalling pathways, such as Peroxisome proliferated activated receptors (PPARs), AMP-Activated protein kinase (AMPK), GLUT4 and Nrf2 pathways. Nikzamir *et al*., (108) reported the down regulation of blood glucose through the unregulated expression of GLUT4 gene levels in the skeletal muscle of rodent model. In another study, cinnamaldehyde was observed to have inhibited protein tyrosine phosphatase-1B (PTP-1B), thereby preventing type II diabetes and obesity (90). Cinnamaldehyde boost the antioxidant protection against reactive species under hyperglycemic conditions, which protects the pancreatic beta cells from damages/loss and exhibited hyperglycemic effect (109). In a chemically-induced diabetic rat model, cinnamaldehyde was reported to exhibit hypoglycemic effect against gestational diabetes through modulating PPARγ (110). In a recent study by Zhao *et al.* (111), it was reported that cinnamaldehyde improved glucose metabolism and insulin sensitivity, increased glycogen synthesis in Type 1 diabetes (T1DM). It also regulated the gut microbiota by causing an increase in Lactobacillus johnsonii and decrease in *Lactobacillus murinus* in T1DM mice. Glucose-6-phosphate dehydrogenase, an enzyme involved in glucose metabolism was observed to have increased activity because of cinnamaldehyde (112). With the potential of cinnamaldehyde as a possible candidate, there is the need for community based trials and clinical studies to better understand the antidiabetic and hypoglycemic effect of cinnamaldehyde.

Anti cancer activity of cinnamaldehyde

Cancer is widely referred to as the uncontrolled proliferation of cells that ultimately causes cell aggregation leading the formation of tumours. It is one of the main causes of death yearly. Different factors are linked to the onset of cancers such genetic mutations, smoking, ingestion of pesticides and heavy metals and unhealthy dietary lifestyle. Cellular aggregation from inflammation due to disruption in the proper functioning of signalling pathways eventually results in pathogenesis of cancers. Thus, treatment of cancer depends on the inhibition of cell proliferation and destruction of malicious cells. Selective destruction of tumour cells without affecting normal healthy cells is the target for cancer chemotherapy. Plant sources with anticancer benefits can interfere with possible targets involved with carcinogenesis and tumour cell biology which make them promising tools in cancer research. A number of studies have reported the chemotherapeutic potentials of cinnamaldehyde against various forms of cancers. Various studies have provided scientific proofs of cinnamaldehyde against breast cancer, prostate cancer, lung cancer, colon cancer, hepatocellular carcinoma (113). Cinnamaldehyde exhibits anticancer activity by inducing apoptosis, inhibiting cell viability and proliferation in a dose dependent manner. *In vitro* studies using breast cancer cell lines by Liu *et al* (114) reported inhibition of cell proliferation by cinnamaldehyde with IC_{50} of 16 µg/ml and 12.23 µg/ml at 24 h and 4 h respectively. In vitro and *in vivo* study executed by Chiang *et al*., (115) reported cinnamaldehyde as the first scientifically demonstrated natural compound to inhibit extracellular and intracellular nicotinamide phosphorylase transferase (NAMPT) in reducing visfatin-induced breast can progression. In an *in vitro* study, cinnamaldehyde was reported to induce autophagy mediated cell death through the endoplasmic reticulum stress and epigenetic modifications in gastric cancer (96).

Anti-neurodegenerative activity of cinnamaldehyde

Neurodegenerative diseases are a group of disorders associated with alteration in neuronal normal functions. They are characterized by progressive degeneration and eventual loss of specific neurons. Neurons make up the nervous system which includes the brain and spinal cord and the inability of neurons to reproduce or replace themselves, makes neurodegenerative diseases incurable. They include Alzheimer's disease, Parkinson's disease, Prion disease, Huntington's disease etc. Cinnamaldehyde has been reported to play important role in reducing neuronal loss and increase the activity of important enzymes in the brain. A study carried out in mouse model of Parkinson's diseases reveals that cinnamaldehyde reduces the dopaminergic neuronal loss in substantia nigra and increases the activity of catalase in the midbrain (116). A major hallmark of Alzheimer's disease is the accumulation of amyloid-β. Cinnamaldehyde has been reported to inhibit its formation through its action on the first rate limiting enzyme β-secretase (BACE-1) in amyloid-β production. Cinnamaldehyde decrease the level of BACE-1 in 5XFAD transgenic mice (98).

Applications of Cinnamaldeyde in Health and Medicine

In health and medicine, cinnamaldehyde has proven to influence diabetics in animals and therefore a potential for diabetic intervention in humans (117). It is also applied to traditional medicine to control blood pressure, tumor growth, diabetics, Alzheimer's, and Parkinson's diseases (118). Cinnamaldehyde has the potential to be applied in skin wounds to quicken the healing process (119, 120) and in cancer chemotherapy (113).

Agriculture

Cinnamaldehyde is applied in the agricultural industry in various ways. It is applied to main the postharvest storage of horticultural crops and maintains the quality of fresh produce (13, 121). It is also used in food preservation as Duan et al (122) demonstrated its potential in preserving citrus from green mold. In addition, it is also applied to agriculture for its food preservation and storage quality and to improve the overall quality properties in fruits (123). It is applied in plant breeding to improve the crops architecture for better adaptation to biotic and abiotic stress. Xue *et al* (124) demonstrated this by applying cinnamaldehyde to plants for lateral root formation. Cinnamaldehyde is also applied in agriculture for its potential and use as a pesticide, herbicide, and weedicide (125, 126). It is used in the control of plant diseases and pests in crops in field and during storage of fruits and vegetables (127).

Food and other Industries

It is applied in the food industry as an effective and promising substitute for chemical synthetic preservative to increase the shelf life of baked food (128). Cinnamaldehyde is also applied as an antifungal agent in food preservation (12). Cinnamaldehyde is applied in the food and beverages, as an odor agent and flavouring agent. Cinnamaldehyde is used in the food industry to reduce the antimicrobial load in packaged food and increase the shelf life of packaged food (129). It is also used as a natural wood preservative (130).

Conclusion

This review article elucidates the use and effectiveness of cinnamaldehyde which can be applied to various areas such as medicine, agriculture, food and other industrial purposes. Cinnamaldehyde contains considerable antimicrobial and antifungal properties and can be applied to inhibit the growth of microbes and fungi in food. Cinnamaldehyde has sparked interest in research as its usefulness is seen especially as an anticancer agent. Nevertheless, more studies are required to specify the dosage of cinnamaldehyde for various applications and to also explore other hidden potentials for the benefit of mankind.

Conflict of Interest

None declared.

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