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REVIEW ARTICLE

Clinical Aspects on the Toxicity of Cinnamon Extracts: A Mini Review

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Abstract

Objective: The current review identifies the adverse and beneficial effects of cinnamon and its components. **Method:** Literature search using online databases including PubMed, Hindawi, ScienceDirect, ResearchGate, and Elsevier were explored. The keywords used for the literature search included cinnamon, cinnamaldehyde, trans-cinnamaldehyde, cinnamon and stroke, cinnamon and antioxidant, and cinnamon and toxic effects. The inclusion criteria for this review encompassed studies that focused on neuroinflammation and neuroprotection, as well as those that examined the effects of stroke. Additionally, the criteria included studies that investigated experiments on ischemic hemorrhage, encompassing both in vivo and in vitro settings. **Findings:** The comparative analysis of studies reveals that cinnamon demonstrates potent antioxidant, anticholinergic, and antidiabetic effects. Cinnamaldehyde exhibits inhibitory effects on collagen and thrombin-induced platelet aggregation, as well as collagen-epinephrine-induced acute pulmonary thromboembolism, suggesting its antithrombotic properties. Moreover, transcinnamaldehyde reduces the brain infarct area by downregulating the gene expression of iNOS, COX-2, and TNF-alpha, thus reducing inflammation associated with ischemic stroke. Additionally, the literature review highlights the neuroprotective properties of cinnamon in treating Alzheimer's disease and Parkinson's disease. Consequently, further research is required to elucidate the potential mechanisms through which cinnamon provides neuroprotection and its efficacy in stroke treatment. **Novelty:** The review reiterates for bioactive compounds present in cinnamon which show promising potential in the treatment of neurodegenerative disorders and stroke.

Keywords: Cinnamon; Trans Cinnamaldehyde; Stroke; Neuroprotection; Anti-oxidant; Anti-inflammation

1 Introduction

Ayurvedic and siddha medicine frequently uses natural sources including herbs, oils, powders, and other natural substances. The traditional belief, though incorrect, is that

natural sources have no negative side effects. Cinnamon is a typical spice that is used in cooking all over the world from ancient times. Cinnamon (*Cinnamomum verum*), also called Ceylon cinnamon, the laurel family (Lauraceae), and the spice derived from its bark. The various species of cinnamon are Chinese cassia (*Cinnamomum cassia*), Vietnamese or Saigon cinnamon (*C. loureiroi*), Indonesian cinnamon (*C. burmannii*), and Malabar cinnamon (*C. citriodorum*).

Cinnamon, plays an important role as a multi-purpose medicinal spice in the modern medicine system. Cinnamon has a good antitumor and immunostimulatory potencies may be attributed as a bright anticancer nominee [1]. The findings provided scientific support for the plant's usage in traditional medicine to treat diabetes and its consequences by showing improved mitochondrial enzymes, hepatic marker enzymes, renal marker enzymes [2]. Cinnamaldehyde, eugenol, volatile oils and oleoresin, derivatives like cinnamaldehyde, cinnamic acid and cinnamate are majorly present in cinnamon [3–5]. Cinnamon exhibits anti- inflammatory activity, potent antioxidant, anticholinergic, and antidiabetic due to its high phenolic content [6,7]. It lowers oxidative stress and lowers risk factors for diabetes and cardiovascular disease [8]. Cinnamaldehyde demonstrated a potent inhibitor of NO generation [9]. Cinnamaldehyde can inhibit blood platelet aggregation [10]. Cinnamon has stronger effects on blood coagulation by decreasing platelet function [11,12]. Trans-cinnamaldehyde possess strong anti-inflammatory properties by reducing neuroinflammatory reactions in BV2 microglial cells, nuclear factor kappa B signaling pathway [13]. Cinnamon reduces neuroinflammation by blocking nuclear factor-kB activation [14]. Cinnamon polyphenol extract decreases infarct and edema formation in traumatic brain injury [15]. Cinnamaldehyde limits neutrophil recruitment, lowering reactive oxygen species, minimizing histologic damage, and alleviating acute hippocampal dysfunction and exhibits neuroprotective effects [16]. Transcinnamaldehyde reduces memory impairment by disrupting nitrous oxide synthase mRNA [17]. Cinnamaldehyde exhibits neuroprotective effects in AD and PD [18]. Cinnamaldehyde activates the mitogen activated protein kinase pathways and kinase activate protein kinases and decreases the inflammatory factors these by helps in neuroprotection [18]. Cinnamaldehyde acts against subarachnoid haemorrhage and stops vasoplasm. It helps protects neurons and dilates blood vessels [19].

We sought to determine whether cinnamon treatment could reduce post ischemic accumulation of ROS and consequently decrease membrane lipid peroxidation, DNA hydroxylation and post ischemic inflammation in the ischemic brain. Despite the fact that cinnamon provides a number of medicinal advantages, the present study shows, cinnamon has neuroinflammation and neuroprotective properties that can help prevent stroke and brain damage in postischemic situations, but more research is needed to fully understand its benefits.

2 Methodology

For the purpose of assessing the safety and toxicity of trans cinnamaldehyde, the current literature used a variety of data bases. The comparative analysis was made using PRISMA flow diagram (Figure 1).

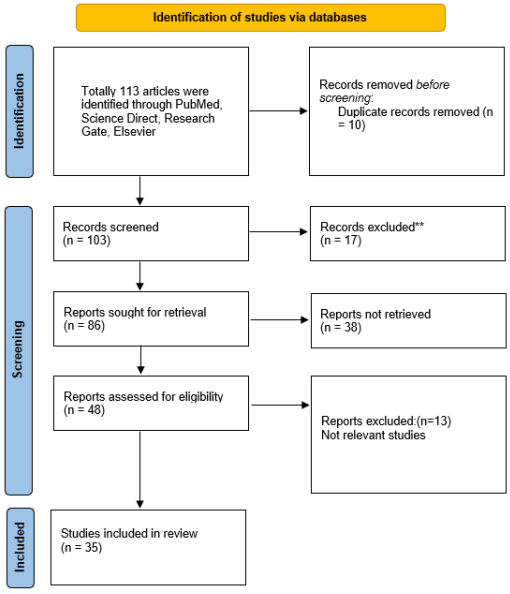

Fig 1. PRISMA Flow Diagram

3 Results and Discussion

3.1 Chemical Constituents and Phyto Chemistry

The major components of cinnamon are eugenol (87.3%) followed by bicyclogermacrene (3.6%), a-phellanderene (1.9%), b-carryophyllene (1.9%), aromadendrene (1.1%), p-cymene (0.7%) and 1,8-cineole (0.7%) [3,4]. Cinnamon consists of many resinous compounds, such as cinnamaldehyde, cinnamate, cinnamic acid, and numerous essential oils [5]. The oleoresins accounted for 97.1% of the total amount. The primary compounds in cinnamon bark volatile oil are I-cinnamaldehyde (49.9%), coumarin (16.6%), d-cadinene (7.8%), a-copaene (4.6%), (Z)-cinnamaldehyde (1.5%), ortho-methoxy cinnamaldehyde (1.5%) and b-bisabolene (1.4%) [4].Other essential oils such as trans-cinnamaldehyde, cinnamyl acetate, eugenol, L-borneol, caryophyllene oxide, b-caryophyllene, L-bornyl acetate, E-nerolidol, α-cubebene, α-terpineol, terpinolene, and α-thujene, have also been reported [6]

3.2 Literature Review of Potential Beneficial Biological Effects of Cinnamon and its Constituents

- **Antioxidant, anticholinergic and antidiabetic effects**

Both ethanolic and aqueous extracts of cinnamon (*Cinnamomum verum*) have been shown to possess inhibitory actions against acetylcholinesterase, butyrylcholinesterase, glycosidase, and amylase [7]. According to the LC;MS/MS study, cinnamon contains pyrogallol, ferulic acid, and p-coumaric acid in the ethanolic extract, along with p-hydroxybenzoic acid, p-coumaric acid, and pyrogallol in the aqueous extract. These compounds are well known antioxidants. Cinnamon is also reported to a potent antioxidant, anticholinergic, and antidiabetic due to its high phenolic content [7].

The onset of diabetes and cardiovascular disease is significantly impacted by oxidative stress, which is enhanced in obesity. Incorporation of cinnamon in the diet of obese individuals reduces the oxidative stress and reduce the risk factors associated with diabetes and cardiovascular disease [8].

- **Free Radical scavenging effects**

The chemical constituents from the cinnamon have been shown to possess scavenging effects against free oxygen and nitric oxide (NO) radicals. Nitric oxide (NO), an endogenous free radical species produced by nitric acid synthase, which in higher concentration can cause cytotoxicity, tissue damage, inflammation, sepsis, and stroke. Notably the essential oil of cinnamaldehyde demonstrated a inhibitory effect on the generation of nitric oxide; due to the presence of trans cinnamaldehyde [9].

Pro-inflammatory cytokines and oxidative stress have been linked to the development of cytotoxic brain edema during cerebral ischemia. Persistent cytotoxic edema may lead to endothelial cell swelling contributing to a leaky blood-brain barrier, which could potentially lead to vasogenic edema. Mitochondrial free radicals, cell swelling and the disruption of inner mitochondrial membrane potential induced by oxygen-glucose deprivation were all mitigated by the polyphenol trimer found in cinnamon (cinnamtannin D1). These polyphenols may lessen endothelial cell edema by decreasing intracellular calcium levels $[Ca^{2+}]i$ [10].

Liver plays a vital role in various metabolic functions, including digestion, detoxification, synthesis of proteins and biochemicals. It also plays a major role in the biotransformation of xenobiotics, which leads to generate free radicals results in lipid peroxidation which ultimately leads to membrane damage. Cinnamaldehyde, an active compound present in cinnamon, is reported to inhibit the metanil yellow hepatotoxic toxic effects and has a positive effect on hepatocytes, thereby mitigating the oxidative stress [11]. Sharma et al [12] reported the increased free radical production is the cause of the nephrotoxicity caused by metanil yellow-induced oxidative stress and administration of cinnamaldehyde, a phenyl propnoid a main constituent of cinnamon, can alleviate oxidative stress [12].

- **Anti-thrombotic effects**

In vitro experiments have demonstrated that cinnamaldehyde can inhibit the platelet aggregation induced by collagen, arachidonic acid and adenosine diphosphate as well as the conversion of fibrinogen to fibrin by thrombin [13]. Cinnamaldehyde also decreased the formation of metabolites of arachidonic acid in collagen-stimulated washed platelets such as thromboxane B2, 12-hydroxyheptadecatrienoic acid hydroxyeicosatetraenoic acid [14].

Huang et al., [15] showed that cinnamaldehyde inhibited collagen- and thrombin-induced platelet aggregation in vitro in a concentration-dependent manner. In mice, cinnamaldehyde administration markedly prolonged hemorrhage and coagulation times and effectively reduced the mortality rate of collagen-epinephrine-induced acute pulmonary thromboembolism. In

an arteriovenous shunt thrombosis rat model, cinnamaldehyde administration for 10 days, dose dependently decreased the thrombus weight. Administration of cinnamaldehyde also significantly inhibited collagen-induced platelet aggregation in the rat platelet-rich plasma (PRP). Hossein et al [16] studied the test of blood coagulation time determination through tube test method and the results indicates that the blood clotting time was significantly decreased in the presence of cinnamon distillate and the essential oil, when compared with control. Among the existing data within this study, the distillate and essential oil of cinnamon have stronger effects on coagulation than water and hydro alcoholic extract [16]. A comprehensive review revealed that cinnamon extract can decrease platelet function and therefore is utilised as a supplemental therapy for cardiovascular disorders [20].

- **Anti-inflammatory effects**

Cinnamon has the potential to be a beneficial therapy in the treatment of disorders accompanied by inflammation and pain. It has anti-nociceptive and anti-inflammatory properties [21]. Several medically significant bioactive characteristics of Ceylon cinnamon, include anti-inflammatory, antilipidemic, and cancer-related actions [22]. Cinnamon does not increase the risk of injury or fatality, or any other adverse effects [23]. Cinnamon's antioxidant and anti-inflammatory characteristics allow it to be used as a safe preventive and therapeutic agent against neurological illnesses such migraine, Attention deficit hyperactivity disorder, Alzheimer's disease, Parkinson's disease, and neuroinflammation. Trans-cinnamaldehyde (TCA), cinnamaldehyde, and eugenol, which are all components of cinnamon, may have additional neuroprotective properties [24]. An good anti-inflammatory agent is cinnamon oil. Several compounds found in the essential oil of the Cinnamomum osmophloeum twig, including trans-cinnamaldehyde, caryophyllene oxide, L-borneol, L-bornyl acetate, eugenol, -caryophylene, E-nerolidol, and cinnamyl acetate, showed excellent anti-inflammatory properties by reducing the formation of nitric oxide by LPS-stimulated macrophages [6].

- **Neuro-inflammation inhibitory effects**

Cinnamon constituents have been shown to inhibit neuroinflammation *in vitro* as well as *in vivo*. Predominantly these actions are mediated by cinnamon derivative's antioxidant and free radical scavenging activities.

In neurodegenerative conditions like Alzheimer's and Parkinson's disease, microglial activation contributes to neuroinflammation and neuronal death. If neuroinflammation can be managed, outcomes of neurodegenerative diseases may be improved. Strong anti-inflammatory properties possessed by trans-cinnamaldehyde enhances the survival of neurons by reducing neuroinflammatory reactions in BV2 microglial cells. trans-cinnamaldehyde reduced neuroinflammation and microglial activation by inhibiting the nuclear factor kappa B signaling pathway [18].

Uncontrollably activated microglial cells can lead to neuroinflammation, which is a major factor in the emergence of neurodegenerative disorders. In lipopolysaccride-activated BV2 microglia, cinnamon extract dramatically reduced the synthesis and expression of nitric oxide (NO), interleukin (IL)-1b, IL-6, and tumour necrosis factor (TNF)-a. Cinnamon's ability to reduce neuroinflammation most likely resulted from blocking the activation of nuclear factor-kB. The most effective anti-neuroinflammatory compound in cinnamon extract reported in this study was cinnamaldehyde [19].

Yulug et al [25] demonstrated the administration of cinnamon polyphenol extract, showed the neuroprotective benefits of cinnamon extract in traumatic brain injury. It significantly decreased the infarct and edema formation that were linked to significant changes in inflammatory and oxidative parameters, such as NF-kB, interleukin 1-beta, interleukin 6, nuclear factor erythroid 2-related factor 2, glial fibrillary acidic protein, neural cell adhesion molecule, malondialdehyde, superoxide dismutase, catalase, and glutathione peroxidase.

Traumatic brain injury can seriously impair brain function and cause a number of ischemic pathologic changes in the brain's tissue. Cinnamaldehyde has demonstrated neuroprotective effects by limiting neutrophil recruitment, lowering reactive oxygen species, minimizing histologic damage, and alleviating acute hippocampal dysfunction [26].

Trans-cinnamaldehyde was studied for its anti-inflammatory and neuroprotective properties. The lipopolysaccharide-induced inflammatory BV2 microglial cells' up-regulation of cyclo-oxygenase-2 and inducible nitric oxide synthase was reduced by transcinnamaldehyde. On dopaminergic neurons, trans-cinnamaldehyde has a neuroprotective effect that may be related to the suppression of inflammatory reactions. These results imply that trans-cinnamaldehyde may be a therapeutic candidate for the avoidance of neurodegenerative disorders brought on by inflammation [27].

In mice with neuroinflammation, trans cinnamaldehyde reduced memory impairment via reducing microglial activation by disrupting nitrous oxide synthase mRNA [17]. The aqueous extract of Cinnamomum cassia Blume prevents glutamate-induced neuronal death by reducing the Ca^2 influx [28].

Trans-cinnamaldehyde is also known for its anticancer, and antioxidant properties. It dramatically decreased the production of Nitric Oxide (NO) and Reactive oxygen species (ROS) [29] .

Trans cinnamaldehyde therapy restored tau-protein hyperphosphorylation and aberrant synaptic protein expression in the hippocampus and prefrontal cortex of PS cDKO double knock out mice. Trans cinnamaldehyde therapy also improved PS cDKO mouse hippocampus long-term potentiation induction and NMDA receptor dysfunction. This compound also inhibits neuroinflammatory responses by lowering pro-inflammatory mediator levels and microglial activation in the hippocampus and prefrontal cortex of PS cDKO mice. Importantly, trans cinnamaldehyde's interrupting effect on the nuclear factor kappa B (NF-B) signaling pathway resulted in the regulation of neuroinflammatory responses, which improved NMDA receptor dysfunction and memory deficits in PS cDKO mice [30].

Cinnamic aldehyde blocks the autophagy of the neuronal cells from the toxic effect of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine by stopping the stimulation pf microtubule associated protein light chain 3(LC3) and increases the down regulation of p62 there by blocking the autophagy inhibitors in the neurodegenerative disorder Parkinson's disease [31]. Cinnamaldehyde had been identified to be anti-inflammatory; it oligomerizes the TLR4 signaling, thereby inhibiting the activation of NFkB and IRF3 induced by LPS, which results in lessen the expression of COX-2 and IFNb in macrophages [32]. This compound also upregulates Nrf2 activation and downstream target proteins thereby protects the endothelial dysfunction under high glucose conditions, which is why the administration of cinnamon enhances cardiovascular protection in high glucose conditions [33]. A growing body of research supports the idea that cinnamaldehyde exhibits neuroprotective effects in animal models of Alzheimer's disease and Parkinson disease by reducing neuroinflammation, reducing oxidative stress, and enhancing synaptic connectivity. The actions of cinnamaldehyde on numerous signaling pathways, such as the TLR4/NF-B, NLRP3, ERK1/2-MEK, NO, and Nrf2 pathways, are what cause these effects. Cinnamaldehyde and its derivatives improve pathogenic alterations in these diseases [34].

The neuroprotective benefits of cinnamon polyphenols may be attributed to their actions on upregulating prosurvival proteins, activating mitogen-activated protein kinase pathways, and reducing proinflammatory cytokines. Additionally, cinnamon polyphenols increased the levels of phospho-p38, an extracellular signal-regulated protein, as well as mitogen-activated protein and kinase-activated protein kinases, all of which may have a role in prosurvival activities. Cinnamon polyphenols increased the protein levels of sirtuins 1, 2, and 3, deacetylases vital to cell viability, and the tumour suppressor protein, p53, while decreasing the amounts of phospho-p65, a nuclear factor-kb component, and inflammatory factors such as tumour necrosis factor alpha [35].

Cinnamaldehyde displays neuroprotective action against early brain injury brought on by subarachnoid haemorrhage, and it can stop vasospasm. Treatment for subarachnoid haemorrhage may be influenced by the methods through which cinnamaldehyde protects neurons and dilates blood vessels [36].

A transcription factor called Nuclear Factor controls the expression of immunological and inflammatory genes. Along with NF-kB transcriptional activity, LPS-induced DNA binding activity of NF-kB was reduced by trans- and 2-methoxycinnamaldehyde [37].

The neurological impairment ratings, cerebral edema, and infarct volume were all decreased with cinnamaldehyde. After cerebral ischemia, cinnamaldehyde attenuated the elevated levels of TNF-, IL-1, CCL2, and endothelial-leukocyte adhesion molecule-1 and, as a result, decreased leukocyte infiltration into the ischemic brain regions. These signal transduction molecules included toll-like receptor 4, tumor necrosis receptor-associated factor 6, and NF- Zhao et al., showed cinnamaldehyde reduces the expression of toll-like receptor 4, tumor necrosis receptor-associated factor 6, and nuclear translocation of NF-B, which in turn inhibits inflammation and protects against cerebral ischemia injury [38].

Cinnamaldehyde reduced the selective dopaminergic neuronal death that occurred in the substantia nigra of 1,1,1,2-,3,6,-tetrahydropyridine (MPTP) mice models. The effect of cinnamaldehyde on the MPTP-mediated stimulation of LC3 puncta, which is a microtubule-associated protein, was diminished. Additionally, cinnamaldehyde treatment increased down;regulated p62; regulated p62 in the substantia nigra of MPTP animals. These findings collectively imply that CA has neuroprotective effects in PD models [39].

Chen et al [39] reported that an essential oil found in cinnamon powder, trans-cinnamaldehyde, dramatically decreased the infarct size in a rat model of cerebral ischemia. By decreasing the NF-jB and p53 pathways and downregulating the gene expression of iNOS, COX-2, and TNF-a, it reduced the generation of nitric oxide and reduced inflammation. Trans-cinnamaldehyde may be a promising therapeutic treatment for reducing inflammation related to ischemic stroke based on the *in vivo* and *in vitro* outcomes.

Available in-vitro and in-vivo research indicate that cinnamon has numerous positive health impacts. To ascertain whether these impacts have any bearing on public health, randomized controlled trials in people will be required owing to the lack of data on humans.

4 Conclusion

Cinnamon is renowned for its insecticidal, therapeutic, and bioactive properties, as well as its health benefits in combating common diseases and disorders. Rigorous preclinical and clinical trials are required to validate its efficacy in the therapeutic and preventive use for clinical disorders and diseases. Trans-cinnamaldehyde (TCA) is a primary bioactive component possesses potent anti-inflammatory and neuroprotective activities by diminishing microglial activation and levels of pro inflammatory mediators and interrupts the nuclear factor kappa B (NF-κB) signaling pathway. TCA can inhibit the Nitric oxide production and inhibits the inflammation by downregulating the gene expression of iNOS, COX-2 and TNF α, suppressing the NF – κB and p53 pathways. It also attenuates the protein expression level of iNOS and COX-2. Inhibit COX-2 protein levels, expression of COX-2 mRNA and TNF α mRNA. TCA reduces infract area in cerebral ischemia mouse model. COX-2 highly expressed in the cells affected by various factors inflammation or tumor such as oncogenes, cytokines, growth factor, endotoxin, carcinogen, catalyzes prostaglandin E 2 (PGE2). Ceylon cinnamon leaf possesses cyclooxygenases inhibition by mediate the COX – 2 expression. The effects of cinnamon on neurological diseases and diabetes have been extensively studied, but additional investigations are essential to provide robust clinical evidence. Moreover, it is crucial to prioritize and evaluate the toxicological effects of cinnamon on human health.

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