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REVIEW ARTICLES

Sinapic Acid: Is It Safe for Humans?

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Sinapic Acid: Is It Safe for Humans?

SUMMARY

Phenolic compounds, one of the most commonly occurring groups of phytochemicals, play an important role in the growth and reproduction of plants, providing protection against pathogens and predators, also contributing towards the colour and sensory characteristics of fruits and vegetables. In humans, it is also suggested to have antioxidant, anti-inflammatory, antimicrobial, anticancer, and cardioprotective effects. Sinapic acid is a small naturally occurring hydroxycinnamic acid derivative. It is a phenolic compound and a member of the phenylpropanoid family which are assumed as therapeutically beneficial and generally non-toxic. Sinapic acid is widespread in the plant kingdom (fruits, vegetables, cereal grains, oilseed crops, some spices and medicinal plants) and in human diet. Derivatives of sinapic acid are characteristic compounds in the Brassicaceae family. Sinapic acid shows antioxidant, antimicrobial, anti-inflammatory, anticancer, and anxiolytic activities. Mainly due to their antioxidative activities, these compounds have been suggested for potential use in food processing, cosmetics, and pharmaceutical industry. In this review, the pharmacological effect, toxicity and safety profile of sinapic acid were assessed.

Key Words: *Phenolic compounds, sinapic acid, Pharmacokinetic effects, pharmacological effects, toxicity, safety.*

Sinapik asit: İnsanlarda güvenli mi?

ÖZET

En yaygın görülen fitokimyasal madde gruplarından biri olan fenolik bileşikler, meyve ve sebzeleri asalak ve patojenlere karşı korumanın yanı sıra, renk ve duyusal özelliklerine de katkıda bulunarak, bitkilerin üreme ve büyümesinde önemli bir rol oynarlar. İnsanlarda da fenolik bileşiklerin antioksidan, antiinflamatuvar, antimikrobiyal, kalp koruyucu ve antikanser etkileri olduğu iddia edilmektedir. Sinapik asit doğal olarak oluşan ufak bir hidroksisinamik asit türevidir. Sağlığa faydalı ve genel olarak toksik olmadığı varsayılan fenilpropanoid ailesinden bir fenolik bileşiktir. Sinapik asit bitki dünyasında (meyve, sebze, tahıl taneleri, yağlı tohumlu bitkiler, bazı baharatlar ve şifalı bitkiler) ve insan diyetinde yaygın bulunur. Sinapik asit türevleri Brassicaceae familyasındaki karakteristik bileşiklerdir. Sinapik asit, antioksidan, antimikrobiyal, anti-inflamatuvar, antikanser ve anksiyolitik aktivite gösterir. Çoğunlukla antioksidan aktiviteleri nedeniyle, sinapik asit ve türevlerinin gıda işleme, kozmetik ve ilaç endüstrisinde potansiyel kullanımı önerilmektedir. Bu derlemede sinapik asitin farmakolojik etkileri, toksisitesi ve güvenlik profili değerlendirilmiştir.

Anahtar kelimeler: *Fenolik bileşikler, sinapik asit, farmakokinetik etkiler, farmakolojik etkiler, toksisite, güvenlilik.*

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INTRODUCTION

Sinapic acid

Phenolic compounds are a group of key plant metabolites found abundantly in fruit and vegetables. Because of their antioxidant properties, they play an important role in preventing various degenerative disorders or diseases related to oxidative damage. Phenolic compounds exhibit a wide range of physiological properties, such as antiallergic, antiatherogenic, antiinflammatory, antimicrobial, antioxidant, antithrombotic, cardioprotective and vasodilatory effects (Tarko *et al*., 2013; Aydin *et al.,* 2015; Tokaç *et al*., 2014).

Phenolic compounds, ubiquitous in plants, are essential parts of human diet, and are of considerable interest due to their antioxidant properties. These compounds possess an aromatic ring bearing one or more hydroxyl groups and their structures may range from that of a simple phenolic molecule to that of a complex high-molecular weight polymer (Bravo, 1998). The antioxidant activity of phenolic compounds depends on the structure, in particular the number and the positions of the hydroxyl groups and the nature of substitutions on the aromatic rings (Balasundram *et al*., 2006). Phenolic compounds are present as conjugates with mono- and polysaccharides, linked to one or more of the phenolic groups, and may also occur as functional derivatives such as esters and methyl esters. Phenolic acids consist of two subgroups, i.e., the hydroxybenzoic and hydroxycinnamic acids. Hydroxybenzoic acids include gallic, p-hydroxybenzoic, vanillic and syringic acids, which in common have the C_6–C_1 structure. Hydroxycinnamic acids, on the other hand, are aromatic compounds with a three carbon side chain (C_6–C_3), with caffeic, ferulic, p-coumaric and sinapic acids being the most common (Bravo, 1998).

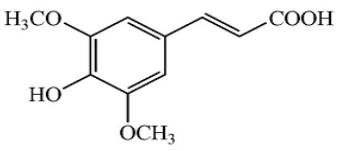
Plant phenolics are biosynthesized by two basic pathways: The shikimic acid pathway and the malonic acid pathway. The shikimic acid pathway participates in the biosynthesis of most plant phenolics. The malonic acid pathway is of more significance in fungi and bacteria than in higher plants (Özeker, 1999). The shikimate pathway leads to the synthesis of aromatic amino acids such as phenylalanine and tyrosine. Hydroxycinnamic acids are formed by the deamination of phenylalanine or tyrosine to yield the C_6–C_3 unit that serves as the core structure of the phenylpropanoids; the deamination is catalyzed by the enzyme phenylalanine ammonia-lyase (Back, 2001). In plants, tyrosine ammonia-lyase converts tyrosine into 4-hydroxycinnamic acid. This pathway is responsible for the biosynthesis of a very large number of diverse secondary metabolites such as lignins (Fukuda ve Komamine, 1982)

Hydroxycinnamic acids (HCAs) are one of the major classes of phenolic compounds found in nature (Herrmann and Nagel, 1989). They have been shown to have beneficial effects in various human diseases, particularly atherosclerosis and cancer. They are secondary metabolites derived from phenylalanine and tyrosine, and they all have a C_6–C_3 carbon skeleton with a double bond in the side chain that may have a cis or a trans configuration. Among the most common and well-known HCAs are cinnamic acid, o-coumaric acid, m-coumaric acid, p-coumaric acid, caffeic acid, ferulic acid, and sinapic acid (El-Seedi et al., 2012). HCAs are widely distributed in the plant kingdom, including many species that are consumed as food or made into beverages, such as fruits, vegetables, and grains (Manach et al*.,* 2004). HCAs can occur freely or as components of plant polymers (Podsędek, 2007). During the past decade, HCAs received particular attention because they are one of the most abundant antioxidants in our diet (Kroon et al.,1999; Eryılmaz et al*.,* 2002)

Sinapic acid is a small naturally occurring hydroxycinnamic acid derivative. It is a phenolic compound and a member of the phenylpropanoid family, the member of which are assumed as therapeutically beneficial and generally not toxic. Sinapic acid is widespread in the plant kingdom (fruits, vegetables, cereal grains, oilseed crops, and some spices and medicinal plants) and is common in human diet. Derivatives of sinapic acid are characteristic compounds of the *Brassicaceae* family. Sinapic acid shows antioxidant, antimicrobial, anti-inflammatory, anticancer, and anxiolytic activity. Mainly due to their antioxidant activity, these compounds have been suggested for potential use in food processing, cosmetics, and the pharmaceutical industry (Nićiforovic and Abramovič, 2014; Chen, 2016).

Chemical and physical properties of sinapic acid

The synonyms of sinapic acid ($C_{11}H_{12}O_5$) (Figure 1) are sinapinic acid; 3,5-dimethoxy-4-hydroxy-trans-cinnamic acid; (2E)-3-(4-hydroxy-3,5-dimethoxyphenyl)-2-propenoic acid; 3-(4-Hydroxy-3,5-dimethoxyphenyl) acrylic acid; trans-4-hydroxy-3,5-dimethoxy-cinnamic acid; trans-sinapinic acid; 4-hydroxy-3,5-dimethoxy-cinnamic acid.



Sinapic acid

Figure 1. Structure of sinapic acid.

Sinapic acid may be found in free form, but also in the ester forms. Hydroxycinnamic esters are found as sugar esters (glycosides), or as esters of a variety of organic compounds (Nićiforovic and Abramovič, 2014). Sinapic acid can also form dimers with itself and ferulic acid in cereal cell walls (Shirley and Chapple, 2003. It is yellow-brown crystalline powder with the molecular weight of 224.21 g/mol. The melting point of sinapic acid is 203-205 °C and it is considered incompatible with strong oxidizing agents, strong bases. It does not dissolve well in water. The most common glycoside of sinapic acid is sinapoyl glucose (1-O-β-D (glucopyranosyl sinapate), which is also found in many Brassicaceae species (Nićiforovic and Abramovič, 2014).

Sinapic acid, undergoes structural changes under the conditions of pressure used during oil extraction from oilseeds and elevated temperature, which result in the formation of 4-vinylsyringol, as well as of syringaldehyde (3,5-dimethoxy-4-hydroxybenzaldehyde) (Cai et al., 1999).

Natural sources of sinapic acid

Sinapic acid is widely distributed in the plant kingdom, it has been identified in various fruits, vegetables, some spices oilseed crops, cereal grains, and medical plants (Nićiforovic and Abramovič, 2014). It has been shown that Citrus fruits contain different amounts of sinapic acid and the fruits of lemon (*Citrus limon L.*) and Murcott orange (*C. reticulate* , *C. sinensis*) have the highest amounts of 72.1 μg/g and 50.1 μg/g on a dry weight basis, respectively (Cartea et al., 2010).

Sinapic acid has been found in various berry fruits such as American cranberries (*Oxycoccus macrocarpus*) with 210 μg/g and strawberries (*Fragaria ananassa L.*) with 450 μg/g (Russell et al., 2009; Zuo et al., 2002). It is also found in significant quantities in cereal grains. Sinapic acid represents 9% to 10% of all phenolic acids and is the most abundant after ferulic acid, in rye (*Secale cereale L.)*. Sinapic acid content may vary between 0.07 and 0.14 μg/g in different rye varieties as well (Andreasen et al., 2000). It is also present in different spices such as dill, anise, rosemary, thyme, sage, basil, capsicum and nutmeg (Herrmann and Nagel, 1989). Sinapic acid and its derivatives are especially particularly abundant in various Brassica vegetables: broccoli, tronchuda cabbage, white cabbage, kale, turnip, radish and leaf mustard (Cartea et al., 2010).

Sinapic acid has been demonstrated that the esters of sinapic acid were the major constituents of the methanolic extract from the radish sprout (*Raphanus sativus L.*) and 3 sinapoyl esters were identified as methyl sinapate, 1,2-disinapoyl-β-D-glucopyranoside, and β-D-(3,4-disinapoyl)fructofuranosyl-α-D-(6-sinapoyl)-glucopyranoside (Takaya et al., 2003). It was found to be the most abundant phenolic acid in kale seeds (*Brassica oleracea convar. acephala*) (including free, ester, glycoside, and ester-bound forms), which represents 52.4% of all phenolic acids. It was also found in the leaves of kale but in a small amounts (Ayaz et al., 2008).

Pharmacokinetics and bioavailability of sinapic acid

It was demonstrated that sinapic acid was absorbed in humans after consumption of a nonprocessed cereal meal, of which the total phenolic content was 3%.. After consumption of the meal, the maximum level of sinapic acid was around 40 nM in plasma and it absorption appears mostly in the small intestine (Kern et al., 2003). The concentration of sinapic acid was reported to be 1.5 μg/mL in human plasma after the consumption of cranberry juice (Zhang and Zuo, 2004).

Sinapic acid is rapidly absorbed from the small intestine when it is in free form. However, phenolic compounds are naturally esterified in plant products, which impairs their absorption (Manach *et al.,* 2004; Shivashankara and Acharya, 2010). Shivashankara et al. (2010) reported that free phenolic acids are 10 to 17 times more bioavailable than esterified phenolic acids in humans. Esterases present in human small intestine and colon can separate the ester bonds and therefore may release some of the hydroxycinnamic acids into the lumen.They can be absorbed afterwards. Furthermore, particular gut bacteria (such as *Bifidobacterium* and *Lactobacillus*), including some already recognized as potentially health-improving, or probiotic have important role in the release of hydroxycinnamic acids from esters and conjugates in human colon (Couteau et al., 2001). The mechanism that involved in the absorption of hydroxycinnamate is not yet well known, because it is unclear if their uptake is passive or active, and if it is dependent on the intact conjugate or requires release of the aglycone at the surface of, or within, the enterocytes (Chesson et al., 1999). According to previous studies, an active Na^+ gradient-driven transport mechanism may exist for cinnamic acid across the intestinal epithelium

(Wolffram et al., 1995). Konishi et al. (2005) has suggested that the across of hydroxycinnamates from human intestinal Caco-2 cells occurs through the transporter of monocarboxylic acid.

Jin et al. (2012) demonstrated that hydroxycinnamic acids were bound to bovine serum albumin mainly by virtue of hydrophobic interaction and hydrogen-bonding. It has been shown that that sinapic acid forms complexes with bovine serum albumin at pH 6.4 by electrostatic forces instead of hydrophobic interactions (Smyk, 2003).

There is limited information on the metabolism of sinapic acid compared to ferulic, caffeic, and p-coumaric acids. In mostly, the metabolism of polyphenols may take place in the liver, intestinal mucosa, kidney, and/or by the intestinal microflora, They can undergo many enzymatic reactions (dehydroxylation, demethylation, dehydrogenation, hydrogenation, o-methylation, glucuronization, glutathione conjugation, sulfation, glycination) during the metabolism (Zhao and Moghadasian, 2010). In an *in vitro* human study, the metabolism of the major dietary hydroxycinnamates, including sinapic acid and its methyl ester was examined by Caco-2 model cells of the human small intestinal epithelium. Enterocyte-like differentiated Caco-2 cells have esterases to deesterify hydroxycinnamate esters (phaseI), and intracellular sulfotransferases and uridine diphosphate glucuronosyltransferases to form the sulfate and the glucuronide conjugates (phase II). This study was performed by free sinapic acid and its methyl ester. The detected metabolites from methyl sinapate were reported to be sinapic acid (a confirmation of esterase activity), methyl sinapate-sulfate, and methyl sinapate-glucuronide (confirmation that methyl sinapate is a substrate for sulfotransferases and UDP glucuronosyltransferases), and the detected metabolites from sinapic acid was found to be only its sulfate conjugate.. After β-glucuronidase treatment, sinapic acid was also recognized as a urinary metabolite, which should be another confirmation of sinapic acid glucuronidation during metabolism, As a conclusion, it is assumed that the human small intestinal epithelium have an important role in the metabolism and the bioavailability of free and esterified sinapic acid which are readly affected in phase I and phase II metabolic reactions (Kern et al., 2003)

Pharmacological effects of sinapic acid

Sinapic acid shows pharmacological effects almost in all systems. Many in vitro and in vivo studies have been conducted to determine the pharmacological properties of sinapic acid and to elucidate mechanism of action of this agent. The majority range of pharmacological activities of sinapic acid has been studied and includes antioxidant, anti-inflammatory, analgesic, anticancer, and antimicrobial (Chen, 2016).

a) Antioxidant activity of sinapic acid

HCAs such as sinapic acid have been described as chain-breaking antioxidants that very likely act as radical scavengers (Cos et al., 2002). This activity is associated with their hydrogen atom donating ability and their ability to stabilize the resulting phenoxyl radicals by means of the conjugated system including the arene and the alkenyl carboxylate side chain (Teixeira et al., 2005).

It has been suggested that sinapic acid is a potent antioxidant and its activity is described as higher than that of ferulic acid (3-methoxy-4-hydroxycinnamic acid) and sometimes comparable to that of caffeic acid (3,4-dihydroxycinnamic acid) (Firuzi et al., 2003). The concern of sinapic acid in cell protection and in oxidative related diseases was reported due to its peroxynitrite (ONOO-) scavenging activity (Niwa et al., 1999; Zou et al., 2002).

It has been shown that sinapic acid at a concentration of 20 μM was able to inhibit 33.2% of the 2,2-diphenyl-1-picrylhydrazyl (DPPH˙) radical (Kikuzaki et al., 2009). It was demonstrated that molar ratio of sinapic acid to (DPPH˙) was 0.5 and sinapic acid was found to show an inhibition of 88.4% being close to the activities of dihydrocaffeic (94.6%), rosmarinic (93.4%), and caffeic acids (92.7%) (Nenadis and Tsimidou, 2002). In a study, the antioxidant activity of an 8–8-bis-lactone-dimer of sinapic acid was measured and found no DPPH˙ scavenging activity at concentrations of lower than 200 μM (Jin et al., 2010). It has been shown that $O_2^{\cdot -}$ scavenging activity of sinapic acid was remarkable (IC_{50} = 17.98 mM) compared to 6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid (Trolox) (IC_{50} = 7.24 mM) which is the well-known antioxidant (Zou et al., 2002).

Sinapic acid scavenged 35.52% of generated $O_2^{\cdot -}$ at 50 μM with IC_{50} values of 979.2 and 70.7 μM, respectively, which demonstrated potent scavenging activity in non-enzymatic (NADH/phenazine methosulfate) and enzymatic (xanthine/xanthine oxidase) $O_2^{\cdot -}$ generating systems, (Jalaludeen and Pari, 2011). It was indicated that the capacity of sinapic acid to scavenge ˙OH radicals (IC_{50} = 3.80 mM) is comparable to that of ascorbic acid (IC_{50} = 4.56 mM) (84). The ONOO– scavenging ability of hydroxycinnamic acids has been examined and it was found that sinapic acid strongly inhibited the formation of 3-nitrotyrosine better than ascorbic acid or α-tocopherol (Niwa et al., 1999). Zou et al. (2002) demonstrated that sinapic acid could efficiently scavenge native ONOO–, as well as ONOO– derived from the peroxynitrite donor 3-morpholinosydnonimine hydrochloride (SIN-1).

Sinapic acid, at the concentration of 500 μmol/kg, was reported to be as same efficient as trolox and butylated hydroxyanisole at the same concentrations and it was fare more efficient than α-tocopherol (Thiyam et al., 2004).

Sinapic acid and the free phenolic fraction of rapeseed meal (having more than 90% of sinapic acid) showed significant inhibition in the formation of hydroperoxides and propanal at concentrations of 500 μmol/kg oil (Thiyam et al., 2006).

Gaspar et al. (2010) examined the antioxidant activities of methyl, ethyl, propyl, and butyl sinapates. to evalute the influence of esterification on the antioxidant efficiency of sinapic acid, In the case of DPPH,˙ sinapic acid itself (IC_{50} = 32.2 μM) showed a higher radical scavenging activity than its alkyl esters (48.7 to 51.9 μM).

The oxidation of low-density lipoprotein (LDL) has been considered to be the important point in the progression of atherosclerosis and other diseases in human (Stocker and Keaney, 2004). Andreasen et al. (2001) demonstrated that sinapic acid decreased LDL oxidation rate significantly, even at the addition level of 10 μM (64% inhibition of conjugated diene formation) and completely blocked oxidation at 20 μM and 40 μM. The high antioxidant activity of sinapic acid was associated with its ability to chelate Cu^{2+} (Hynes and Coinceanainn, 2002). In an another study, sinapic acid demonstrated greater antioxidant activity (28%) than 4 -vinylsyringol (7.5%) at 10 μM concentration, however 4-vinylsyringol (97.1%) was slightly more effective than sinapic acid (95.3%) at the higher concentrations (25 μM) in the LDL model system (Vuorela et al., 2005).

It was found that sinapic acid inhibited AAPH induced hemolysis by 50% at 4.5 μM compared to cinnamic acid or caffeic acid that inhibited AAPH induced hemolysis by 50% at 6.8 and 7.2 μM, respectively. Furthermore, ethyl sinapate had a similar activity to that of sinapic acid (5.0 μM) (Chalas et al., 2001).

b) Antiinflammatory effects of sinapic acid

In an animal study, it has been demonstrated that sinapic acid exert anti-inflammatory effect, resulting from inhibition of lipopolysaccharide (LPS) induced expressions of inducible nitric oxide synthase (iNOS) and cyclooxygase (COX)-2 at the protein levels, and iNOS, COX-2, TNF-R, and IL-1β mRNA expression in RAW 264.7 in a dose dependent manner. The result suggested that the repression of iNOS and COX-2 induction and of the production of proinflammatory cytokines by sinapic acid may have important mechanisms reated to the inhibition of paw edema formation in rats and mice by serotonin or carrageenan (Yun et al., 2008).

c) Anticancer effects of sinapic acid

There is limited data about the anticancer effects of sinapic acid in the literature. According to a study, sinapic acid exerted an inhibitory effect on tumorigenic colon cells, but had a low influence on breast cancer cells. On the other hand, sinapic acid showed also antiproliferative effect on human breast cancer (T47D) cells (Hudson et al., 2000). Supportively, the inhibitory effect was a time- and dose-dependent manner on T47D cancer cells, that were treated by sinapic acid. It decreased cell proliferation by 20%, with an IC_{50} value of 7×10^{-11} M (Kampa et al., 2004).

Antimutagenic effects of 4-vinylsyringol, which is isolated from crude rapeseed oil and pure sinapic acid, was tested by the constant flux method. The mutation was inhibited by sinapic acid (43% at 10 μM and 20% at 100 μM), while 4-vinylsyringol exhibited a potent antimutagenic effect at concentrations >8 μM in a dose dependent manner. The antimutagenic potency of 4-vinylsyringol is calimed to be the result of its $ONOO^-$ scavenging ability. As a result, it was suggested that 4-vinylsyringol suppressed cell damage induced by ONOO, preventing apoptosis of bacterial and mammalian cells, as well as preventing plasmid DNA-strand breakage (Kuwahara et al., 2004).

Antiproliferative and apoptotic effects of selective phenolic acids including sinapic acid were also demonstrated to be a dose dependent and time dependent manner in T47D human breast cancer cells.. It was also shown that the inhibitory effect of sinapic acid on tumoral proliferation might be because of its direct interaction with the aryl hydrocarbon receptor, the nitric oxide synthase inhibition and its pro-apoptotic effect (Kampa et al., 2004).

d) Anxiolytic effects of sinapic acid

It is suggested that sinapic acid is an important anxiolytic (anti-anxiety) agent. Based on electrophysiological investigations, sinapic acid might act like the agonist of a specific gamma-aminobutyric acid (GABA) receptor (ligand-gated ion channel: $GABA_A$). It was found that sianpic acid was the most effective at a dose of 4 mg/kg. It was concluded that the anxiolytic-like effects of sinapic acid are mediated via $GABA_A$ receptors and potentiating Cl^- currents (Yoon et al., 2007).

e) Antimicrobial effects of sinapic acid

The antibacterial activity of sinapic acid has been demonstrated in various studies on both plant and human pathogens. It was found that sinapic acid has inhibitory effects against the growth of *Xylella fastidiosa*, a pathogenic bacterium causing diseases in many crop species which leadis to economic losses (Maddox et al., 2010). It has been showed that sinapic acid has bactericidal activity against *Salmonella enterica ssp. enterica*, which is the most common cause

of human foodborne illness (Johnson et al., 2008).

Sinapic acid isolated from rapeseed was found to be highly effective against the growth of gram-negative (*Escherichia coli, Enterobacter aerogens,* and *Pseudomonas fluorescens*) and gram-positive (*Bacillus subtilis, Bacillus cereus, Streptococcus lactis,* and *Streptococcus cremoris*) bacteria (Nowak et al., 1992).

The antimicrobial activity of sinapic acid to *fastidiosa* strains from different hosts, including grape, coffee, almond was presented as the minimal inhibitory concentration (MIC) and values of 2000 µM and 800 µM were determined. At the concentration of 1 mg/mL, sinapic acid was found to inhibit the growth of *Erwinia carotovora*, which cause decay in stored fruits and vegetables in nutrient broth (Lyon and McGill, 1988).

The MIC of sinapic acid for *Bacillus subtilis, E. coli*, and *Pseudomonas syringae* were 2 mM, 4 mM, and 8 mM, respectively, determined by the microdilution method in nutrient broth (Barber et al., 2000). In another study, MIC values were found as 2.2 mM, 2.0 mM and 1.9 mM (Tesaki et al.,1998).

Engels et al. (2012) approved the antibacterial activity of sinapic acid against *Bacillus subtilis* (MIC = 0.3 g/L), *E. coli* (MIC = 0.7 g/L) and *Staphylococcus aureus* (MIC = 0.3 g/L) and assessed its effects against *Listeria innocua* (MIC = 0.3 g/L), *Listeria monocytogenes* (MIC =0.2 g/L) and *Pseudomonas fluorescens* (MIC = 0.6 g/L) (Engels et al., 2012).

f) Neuroprotective effects of sinapic acid

Acetylcholinesterase (AChE) regulates the concentration of the transmitter by hydrolyzing and inactivating acetylcholine (ACh). Inhibitors of AChE have therapeutic applications in diseases associated with the deficiency of ACh such as Alzheimer's disease, senile dementia, ataxia, myasthenia gravis, and Parkinson's disease. Sinapine (sinapoyl choline) was considered and investigated as a potential AChE inhibitor as a consequence of its structural similarity to ACh (Soreq and Seidman, 2001).

He et al. (2008) reported that sinapine was able to significantly inhibit AChE activity *in vitro*, being more effective in a cerebral homogenate (IC_{50} = 3.66 μM) than in blood serum (IC_{50} = 22.1 μM) of rats. Lee et al. (2012) established that sinapic acid attenuated amyloid β $(Aβ)_{1-42}$ protein-induced Alzheimer's disease. The results suggested that sinapic acid could be used as an effective treatment for Alzheimer's disease.

It was found that sinapic acid (10 mg/kg) decrease kainic acid-induced hippocampal neuronal damage in mice. The results suggested that the potential therapeutic effects of sinapic acid in brain was resulting from its anti-convulsive activity via $GABA_A$ receptor activation and radical scavenging activity (Kim et al., 2010).

It has also been demonstrated that sinapic acid inhibited potassium cyanide (KCN)-induced hypoxia or carotid-artery ligation-induced mortality. In the same study, sinapic acid significantly inhibited CO_2-induced impairment which was suggested that the anti-amnesic effect of sinapic acid maybe achieved by preventing the neuronal death or damage resulting from hypoxia (Karakida et al., 2007).

g) Cardioprotective effects of sinapic acid

In an *in vitro* study on rats, the protective effects of sinapic acid on lysosomal dysfunction in isoproterenol induced myocardial infarcted rats were assessed. Pre-and-co-treatment with sinapic acid (12 mg/kg va) normalized all the biochemical parameters and reduced myocardial infarct size in myocardial infarcted rats (Roy et al., 2012).

h) Hepatoprotective effects of sinapic acid

The hepatoprotective effects of sinapic acid in rats with carbon tetrachloride (CCl_4) induced acute hepatic injury was assessed. Sinapic acid treatment reduced CCl_4-induced abnormalities in the histology of liver, liver malondialdehyde levels, serum aspartate transaminase and alanine transaminase activities.. In addition, sinapic acid treatment significantly reduced the inflammatory mediators production of tumor necrosis factor-alpha, interleukin-1β mRNA levels induced by CCl_4 and increased the expression of nuclear factor-kappa B (NF-κB p65) (Shin et al., 2013).

According to the study by Wilson et. al. (2011), the effects of sinapic acid on certain biochemical markers and histology of liver and kidney in normal and streptozotocin (STZ) -induced diabetes in Wistar rat were evaluated. Oral administration of sinapic acid for a period of 35 days restored all these biochemical parameters (blood urea, serum creatinine, uric acid, total protein and albumin albumin/globulin ratio) and histopathological changes that occurred in liver and kidney to near normal levels. Sinapic acid was suggested to have protective role against arsenic induced toxicity in rats. In the study, rats were orally treated with arsenic alone (5 mg/kg/day) plus sinapic acid at different doses (10, 20 and 40 mg/kg) for 30 days. It was indicated that 40 mg/kg sinapic acid has higher efficacy to normalize hepatic enzymes and histopathology of liver (Pari et al., 2011).

Sinapic acid was reported to have a potential antihyperglycemic effect in streptozotocin -induced diabetic rats. Pre-and-co-treatment with sinapic acid normalized all the biochemical parameters (plasma glucose, insulin, C-peptide, levels of blood hemoglobin, glycosylated hemoglobin, the activities of carbohydrate metabolizing enzymes hexokinase, glucose-6-phosphatase, fructose-1and 6-bisphosphatase) (Kanchana et al., 2011).

Toxic effects of sinapic acid

There are very few studies related to the toxicity of sinapic acid. Sinapic acid has been shown to exert slightly higher cytotoxic activity than of its ester derivate in the superoxide scavenging test (Jin et al., 2010).The treatment of sinapic acid did not induce cytotoxic effects on human neuroblastoma cells (SH-SY5Y) (Kim et al., 2011).

In our previous study, we assessed the cytotoxic profiles of sinapic acid in a wide range of concentrations in Chinese hamster lung fibroblasts (V79) and human cervical carcinoma (HeLa) cells using Neutral Red Uptake assay. The concentrations up to 500 μM and 2000 μM had no effects on the viability of V79 and HeLa cells, respectively. IC50 values were found to be 1860 μM and 7248 μM in V79 and HeLa cells, respectively. This study has shown that sinapic acid have no cytotoxic effects in two different cell lines except at very high concentrations (Hameed et al., 2016).

The effectiveness of sinapic acid as pBR322 plasmid DNA-cleaving agents in the presence of Cu^{2+} ions was investigated. Sinapic acid was remarkably more effective at causing DNA damage than other phenolic compounds toward human promyelocytic leukemia (HL-60) cell proliferation. Addition of exogenous Cu^{2+} ions resulted in an effect dichotomy on cell viability depending on the concentration of sinapic acid, that is, low concentrations of sinapic acid enhanced the cell viability, and conversely, high concentrations of sinapic acid almost completely inhibited the cell proliferation. The good correlation between the DNA damaging activity and the oxidative potential of the sinapic acid indicates that the electron transfer between HCAs and Cu^{2+} plays a crucial role in the reaction (Zheng et al., 2008).The cytoprotective effect of sinapic acid was examined by using both apoptosis and necrosis endpoints. Sinapic acid exhibited protection against H_2O_2-mediated cytotoxicity in a dose dependent manner (Zhang, et al., 2008).

There are many studies on the phenolic compounds for their genotoxic/antigenotoxic effects, however there are not enough data on sinapic acid. Maistro et al. (2011), examined the genotoxic and clastogenic potential of three phenolic compounds such as caffeic, cinnamic and ferulic acids, using the comet and micronucleus (MN) assays *in vitro* in rat hepatoma tissue cells (HTCs). Three different concentrations (50, 500, and 1500 μM) of these phenolic acids were tested on the HTCs for 24 h. The caffeic, cinnamic and ferulic acids were not found to be genotoxic by the comet assay, however, in the MN test an increase in the frequency of micronucleated cells for the three compounds were observed, indicating that these substances have clastogenic effects in HTC.

In an in vitro study, the genotoxic and antigenotoxic effects of sinapic acid were investigated on the growth of human adenocarcinoma colon cells (HT-29) by using comet assay. The result showed that sinapic acid has found to exert antigenotoxic effect on human adenocarcinoma colon cells with EC50 (3.7± 3.1 μmol/L) (Lee-Manion et al., 2009).

Some phenolic compounds were found to be genotoxic but the mechanisms involved in this process are not fully understood. For example, the induction of chromosomal aberrations by phenol, catechol and pyrogallol in V79 cells at different pH values (6.0, 7.4, and 8.0) were observed. Catechol and pyrogallol showed clear clastogenic effect in a pH-dependent way. Taken together, it was suggested that, despite the structural similarity between the different molecules studied, the mechanisms of genotoxicity of these molecules could be considerably different. The existence of several mechanisms of genotoxicity, partially shared by this class of compounds, could explain the synergistic effects observed between these compounds in several genotoxicity test systems (do Céu Silva et al., 2003).

CONCLUSION

Sinapic acid is a small naturally occurring hydroxycinnamic acid derivative. It is a phenolic compound and a member of the phenylpropanoid family. Derivatives of sinapic acid are characteristic compounds of the *Brassicaceae* family. Sinapic acid is common in the human diet and has been suggested to show antioxidant, antimicrobial, anti-inflammatory, anticancer, and anxiolytic activity. Phenolic antioxidant compounds such as sinapic acid are assumed as therapeutically beneficial and generally not toxic, however, there are very few studies related to the toxicity of sinapic acid.

In conclusion, sinapic acid shows pharmacological effects almost in all systems. Several in vitro and in vivo studies have been conducted to determine the pharmacological properties of sinapic acid and to elucidate mechanism of action of this agent. The majority range of pharmacological activities of sinapic acid include antioxidant, antimicrobial, anti-inflammatory, analgesic and anticancer effects. However, there are limited data related to the toxicity of sinapic acid. Sinapic acid have suggested to be not toxic even at high concentrations. It seems that sinapic acid may be a useful for clinical research on the treatment of the diseases related to oxidative damage, which support the ethnopharmacological properties and the traditional medical use of plants having sinapic acid. Further clinical and *in vivo* studies are required to understand the pharmacological properties and toxic effects of sinapic acid in detail.

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