**INTRODUCTION**

There are over 1300 species of *Acacia* (family Mimosaceae), and exudates, leaves, seeds, heartwood, and bark are used in numerous ways. Gum Acacia (gum arabic) has been used for its medicinal properties for approximately 2500 years. It is employed as a demulcent (soothing and protectant agent) and emulsifier, and is used to increase viscosity of solutions and suspensions. It is also used in the food, soft drink, textile, tanning, cosmetic, and confection industries. As a consequence, wide exposure to gum Acacia occurs.

In recent years, numerous studies have examined various pharmacological properties of extracts prepared from heartwood, bark, leaves, seeds, and seed pods of *Acacia* species. This review will focus on the published studies associated with *Acacia catechu* Willd. (Mimosaceae) heartwood extracts, which historically have been known for their high tannin content that is obtained by boiling the heartwood with water and evaporating the solution to prepare the extract. *Acacia catechu* extracts have also played a role in chemistry, with various names of chemicals as catechin, catechol, and catecholamine being derived therefrom.

**CHEMISTRY**

High-performance liquid chromatography coupled with electrospray ionization mass spectroscopy of an aqueous extract of the heartwood and leaves of *A. catechu* has

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**REVIEW**

Antioxidant, Anti-inflammatory, and Chemoprotective Properties of *Acacia catechu* Heartwood Extracts

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Aqueous extracts of *Acacia catechu* heartwood are rich source of catechin and epicatechin (gallic acid derivatives), with smaller amounts of flavonoids. Extracts have also been prepared with ethyl acetate, ethanol, and methanol, and the properties of these extracts have been studied and are reviewed. Potent antioxidant activity has been well established in both *in vitro* and *in vivo* studies. This antioxidant activity is believed to be responsible for the anti-inflammatory, tissue protectant, antineoplastic, and analgesic activities that have been demonstrated and clearly established in animal and cell culture systems. Furthermore, antihyperglycemic, antiarrhythmic, and antiinflammatory activities have been demonstrated in animal studies. No adverse effects have been observed in animal or human studies or in cell culture systems. In spite of the fact that *Acacia* products have been used for many years and the general safety of catechins and epicatechins is well documented, few human studies have ever been conducted on the efficacy or safety of *A. catechu* heartwood extracts. Several studies have shown that a two-ingredient combination product containing *A. catechu* extract exhibited no adverse effects when administered daily for up to 12 weeks while exhibiting significant anti-inflammatory activity in subjects with osteoarthritis of the knee. There is a need for additional human clinical studies with regard to efficacy and safety. © 2015 The Authors. Phytotherapy Research published by John Wiley & Sons Ltd.

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**Keywords:** *Acacia catechu,* heartwood extracts; antioxidant; anti-inflammatory; chemoprotective; antineoplastic; analgesic; *Acacia catechu* heartwood extract; *A. catechu* heartwood extract.

*Acacia catechu* is also known as kattha (Urdu), khadir (Hindustani and Punjabi), khoyer(Bengali and Assamese), khair and babul (Hindi), kaath (Marathi), and kachhu (Malay). It is indigenous in India, other Asian countries, and East Africa. Traditionally, *A. catechu* has been used as an antimicrobial, anti-inflammatory and antifungal, coagulant, vermifuge, antidiarrheal, and astrigent, and has also been employed to heal wounds, treat obesity and diabetes, and maintain oral hygiene, (Chauhan *et al.*, 2011).

*Acacia catechu* heartwood extracts have also been used traditionally in the preparation of betel quid (paan masala), which consists of *Piper betle* leaves, *A. catechu* paste, chopped *Areca* nut, lime, and various spices with or without tobacco (Thomas and Kearsley, 1993; Rahmatullah *et al.*, 2013; Waris and Nagi, 2014). Betel chewing is used to produce euphoria, a sense of well-being, heightened sense of alertness, and psycho-stimulation (Chu, 2001). This review primarily focuses on applications of *A. catechu* heartwood extracts other than its use in conjunction with betel quid.
shown that the primary constituents are catechins (Shen et al., 2006), which by definition are gallic acid (polyhydroxylated benzoic acid) derivatives and polyphenols, flavonal dimers, and caffeine. The predominant catechins in A. catechu include catechin, epicatechin, epicatechin-3-O-gallate, and epigallocatechin-3-O-gallate. Other major secondary products present in the extracts included flavonol glycosides, flavonols, and caffeine.

Other constituents that have been identified in aqueous extracts of A. catechu include rhamnetin, 4-hydroxyphenol, 3,3′,5,5′,7-pentahydroxyflavone, fisetinidol, 5-hydroxy-2′-[2-(4-hydroxyphenyl)acetyl]-3-methoxybenzoic acid, and (2S,3S)-3,7,8,3′-O-pentahydroxyflavane (Li et al., 2011). The presence of high amounts of gallic acid-derived compounds is primarily responsible for the astringent, tanning, and antioxidant properties of the extracts.

An extract from the heartwood of A. catechu was shown to contain 66.9% catechin and 23.1% epicatechin; thus, 90% of the composition of this extract consisted of these two components (Hiraganahalli et al., 2012). Sulaiman and Balachandran (2012) reported that an A. catechu powdered sample is high in gallic acid-related compounds, containing approximately 78 mg gallic acid equivalents per gram as determined by the Folin–Ciocalteu assay.

Hazra et al. (2013) conducted a phytochemical screening of a 70% methanol extract of A. catechu heartwood. The extract was analyzed for the presence of carbohydrates, alkaloids, tannins, ascorbate, terpenoids, triterpenoids, anthraquinones, saponins, and glycosides. The extract contained measurable amounts of tannins (catechins) (20 mg catechin equivalent/100 mg extract), alkaloids, ascorbic acid, and carbohydrates, and also tested positive for terpenoids and triterpenoids as well as glycosides. No anthraquinones or saponins were detected.

### HUMAN STUDIES

Although A. catechu extracts have been widely used for hundreds of years, few published studies involving humans exist. One of the earliest known clinical studies involved an evaluation of A. catechu in the treatment of lepromatous leprosy (Ojha et al., 1969).

Several human studies have assessed the anti-inflammatory effects of a combination of A. catechu extract of heartwood, roots, or bark in combination with a root extract of Scutellaria baicalensis (Chinese skullcap), which has been reviewed by Bitto et al. (2014). The primary studies will be summarized later in the text. A 12-week placebo-controlled, double-blind, randomized safety study was conducted on 59 subjects with moderate osteoarthritis of one knee (Morgan et al., 2009). The product (flavocoxid) that was used consisted of a proprietary blend of the flavonoids and flavanes of the bark of A. catechu and the root of S. baicalensis, and was given at a dose of 250 mg twice a day versus the placebo. At the end of the study, there were no significant differences with respect to laboratory values including blood chemistry, clinical laboratory, blood pressure, or body systems, indicating a high degree of safety of the product at this dose. No efficacy data or information was reported.

In a subsequent study (Levy et al., 2010), the A. catechu plus S. baicalensis extract product (flavocoxid) was assessed for its safety and efficacy in 220 subjects with moderate-to-severe osteoarthritis of the knee using a 12-week double-blind, randomized protocol. The subjects received either the extract product orally or naproxen (both products 500 mg twice daily). At the conclusion of the study, the authors concluded that the botanical extract product was as effective as naproxen in managing the symptoms and signs of osteoarthritis of the knee. Furthermore, the botanical product containing A. catechu exhibited better gastrointestinal, renal, and respiratory safety than naproxen.

Another group of investigators (Arjmandi et al., 2014) conducted a 1-week randomized, double-blind clinical trial in 79 moderately osteoarthritic subjects (ages 40–90 years) to examine the efficacy of UP446, a proprietary blend of A. catechu and S. baicalensis extracts (500 mg/day), to ameliorate knee joint pain and mobility as well as selected biomarkers of inflammation in comparison to naproxen (440 mg/day). Pain, knee range of motion, and overall physical activity were evaluated in all groups. Serum interleukins 1β (IL-1β), interleukin 6 (IL-6), tumor necrosis factor-α (TNF-α), C-reactive protein, and hyaluronic acid were assessed in the fasting blood sample. The combination product exhibited significant efficacy in perceived pain, stiffness, and knee range of motion. This short clinical investigation indicates that this combination product is efficacious in ameliorating the symptoms of knee osteoarthritis.

### IN VITRO ANTIOXIDANT ACTIVITY

A number of studies have examined the antioxidant activity of A. catechu extracts in vitro. Naik et al. (2003) demonstrated that aqueous extracts of various plant parts were capable of inhibiting radiation induced-lipid peroxidation in a rat liver microsomal preparation. Antioxidant activity was also demonstrated against 2,2-diphenyl-1-picyrylhydrazyl (DPPH) radicals and radical formation by pulse radiolysis.

The antioxidant, iron-chelating, and DNA-protective properties of a 70% methanolic extract of A. catechu heartwood were assessed (Hazra et al., 2010). The extract was shown to exhibit free radical-scavenging activity against superoxide, nitric oxide, peroxynitrite, hydrogen peroxide, singlet oxygen, and hypochlorous acid radicals. The extract used had a gallic acid phenolic equivalent of 97 mg/mL and a quercetin equivalent flavonoid content of 383.7 mg/mL.

Guleria et al. (2011) conducted a detailed analysis of the antioxidant activities and ability to protect against DNA strand breaks with methanol, acetone, and ethyl acetate extracts of heartwood, bark, and leaves of A. catechu. The results demonstrated that methanol and ethyl acetate extracts of heartwood exhibited potent antioxidant and DNA-protective activities. A heartwood extract was shown to be effective against DPPH radicals, superoxide anions, and hydroxyl radicals.

Other studies have demonstrated in vitro antioxidant and free radical-scavenging activities of aqueous extracts of A. catechu (Patil et al., 2003; Kumar et al., 2013), A. catechu bark extracts (Sulaiman et al., 2011), and ethyl acetate extracts of the whole plant based on anti-lipid peroxidative activity, superoxide anion-scavenging activity, and reducing power (Noorani et al., 2010). Thus, the antioxidant and radical-scavenging activities of the A. catechu products are plausible for a variety of uses.
activities of heartwood, leaf, and bark extracts are well established.

Methanol and hexane extracts of A. catechu bark were found to be more antiproliferative and cytotoxic than aqueous extracts against various cancer cell lines in vitro (Nadumane, 2011). At the same time, the extracts appeared to be quite safe against human peripheral lymphocytes, suggesting that the results could be extrapolated to humans.

Ghate et al. (2014) assessed the in vitro anticancer and apoptosis efficacy of a 70% methanolic extract of A. catechu heartwood in the cultured MCF-7 human breast adenocarcinoma cell line. The extract exhibited significant cytotoxicity towards cultured MCF-7 cells (IC50 (50% inhibitory concentration) = 289 µg/mL), as well as induced apoptosis as demonstrated by flow cytometric analysis and morphological investigation. Immunoblot analysis confirmed that apoptosis induction by the extract was achieved by enhancing Bax/Bcl-2 ratio with activation of the caspase cascade and ultimate cleavage of poly adeno ribose polymerase.

ANIMAL STUDIES

A number of early studies were conducted on various A. catechu extracts and products. The effect of administering A. catechu on niacin, ascorbic acid, and riboflavin status in rats was examined (Chaudhari and Hatwalne, 1970), followed by a study on the effect of A. catechu on niacin biosynthesis and requirements in rats (Chaudhari and Hatwalne, 1971). The hypoglycemic activity of A. catechu seeds in the diet was also studied (Singh et al., 1976). An aqueous extract of A. catechu heartwood was shown to produce a dose-dependent decrease in blood pressure in both anesthetized dogs and rats (Sham et al., 1984).

The hypoglycemic, hepatoprotective, antipyrexic, and antidiarrheal activities of an ethyl acetate extract of A. catechu heartwood were demonstrated in rats (Ray et al., 2006). A dose of 250 mg/kg orally exhibited significant antidiarrheal properties, while doses of 250 and 500 mg/kg significantly reduced blood sugar levels in alloxan-induced diabetic rats. Similar doses exhibited antipyrexic activity as well as significant protection against carbon tetrachloride-induced liver damage. The antihyperglycemic activity of an A. catechu ethanolic bark extract has also been demonstrated in alloxan-induced diabetic rats (Jarald et al., 2009).

Bhatia et al. (2011) have also shown that an ethanol extract of A. catechu heartwood exhibits antihyperglycemic activity in streptozotocin-induced diabetic rats at a dose of 250 mg/kg. Furthermore, the extract showed marked inhibition of aldose reductase enzyme activity in the eye lens of normal rats. In diabetic animals, glucose is metabolized by this enzyme to sorbitol and fructose, which are believed to contribute to the microvascular complications associated with diabetes.

An ethyl acetate extract of black catechu, a product obtained from A. catechu heartwood, at doses of 250 and 500 mg/kg, was shown to significantly reduce glucose absorption when given orally to rats (Gunindro et al., 2013). The presence of tannins and flavonoids in the product were believed to be responsible for this action. This study represents another mechanism whereby A. catechu extract can control blood sugar levels.

In another investigation, Rahmatullah et al. (2013) evaluated the dose-dependent anti-diabetic and antinociceptive efficacy of an aqueous extract of the heartwood of A. catechu in mice at doses up to 400 mg/kg body weight. A reduction of 37% in serum glucose levels was observed in an oral glucose tolerance test at a dose of 200 mg/kg body weight of the extract. A similar result was seen with a 400 mg/kg dose. In a parallel experiment, the antihyperglycemic drug glibenclamide (10 mg/kg body weight) lowered serum glucose level by 48.6%.

In the antinociceptive efficacy study, an approximately 70% reduction in writhing, induced in mice by intraperitoneal administration of acetic acid, was observed with a dose of 400 mg/kg body weight of the extract (Rahmatullah et al., 2013). In a parallel experiment, the standard antinociceptive drug aspirin at 400 mg/kg body weight reduced the number of writhing by 60.5%. This study indicates that A. catechu heartwood extract is efficacious in reducing blood sugar levels in diabetic mice as well as in the alleviation of pain. The components of the extract responsible for these effects were not determined.

Several studies have demonstrated that ethyl acetate extracts of A. catechu heartwood when given intraperitoneally can protect against carbon tetrachloride-induced liver toxicity (Jayasekhar et al., 1997; Valte et al., 2012). In both studies, doses of the extract were given at 250 mg/kg. In neither case was the effect of oral administration determined.

In another study (Hiraganahalli et al., 2012), the hepatoprotective and antioxidant activity of a standardized extract of A. catechu was evaluated against t-butyl hydroperoxide-induced toxicity in a human hepatocarcinoma cell line. The extract was shown to have significant hepatoprotective activity. Furthermore, the extract was shown to exhibit high antioxidant radical-quenching activity when tested in vitro against four different assay systems. These authors also concluded that the A. catechu heartwood extract has a hepatoprotectant ability, and that this activity was mainly attributable to the antioxidant activity, which reduced lipid peroxidation and cellular damage.

Hazra et al. (2013) investigated the dose-dependent efficacy of a 70% methanol extract of A. catechu heartwood (50, 100, and 200 mg/kg body weight orally) against iron-induced hepatotoxicity in Swiss albino mice over a period of 21 days. Iron-induced hepatotoxicity was induced using five intraperitoneal doses (one dose every 2 days) of iron–dextran solution at 100 mg/kg body weight. Three doses of heartwood extract and a standard oral iron-chelating drug Desirox (20 mg/kg body weight) were given to various groups of mice. The heartwood extract exhibited dose-dependent reductions in hepatic iron, lipid peroxidation, protein carbonyl, liver fibrosis, serum enzymes, and ferritin. The antioxidant enzyme levels including superoxide dismutase, catalase, and glutathione S-transferase as well as reduced glutathione were enhanced, and the reductive release of ferritin iron increased significantly with gradually increasing concentrations of the heartwood extract.

Furthermore, iron overload caused damage to the hepatocellular organelles including mitochondria and lysosomes, and a significant increase in hydroxyproline, a biomarker of hepatic fibrogenesis, was observed (Hazra et al., 2013). The heartwood extract significantly reduced hydroxyproline levels, demonstrating its hepatic fibrosis.
inhibitory potency. Moreover, the iron induced dramatic increases in alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, and bilirubin, all of which were significantly attenuated by the heartwood extract in a dose-dependent manner. The authors also conducted a phytochemical screening of the extract as described in the Section on Chemistry.

Monga et al. (2011, 2013) have conducted a series of studies on the chemoprotective effects of A. catechu heartwood extract in mice. In each of these studies, 7,12-dimethylbenz[a]anthracene (DMBA) or DMBA plus 12-O-tetradecanoylphorbol-13-acetate was used to induce tumors in the mice. In the initial study, various solvents were used with a standardized aqueous extract being further tested because of the results of cytotoxicity testing on a human epithelial carcinoma cell line (Monga et al., 2011). The results showed that DMBA-induced squamous cell carcinomas in mice were inhibited by the aqueous extract in a dose-dependent manner with maximum tumor incidence being decreased by 70%.

In a second study, Monga et al. (2013) evaluated the A. catechu heartwood extract against a human breast adenocarcinoma cell line and DMBA-induced mammary carcinoma in mice. The extract was shown to exhibit a dose-dependent, potent antitumor activity. Furthermore, the extract increased the activities of the antioxidant enzymes superoxide dismutase, catalase, glutathione peroxidase, glutathione transferase, and glutathione reductase. It also increased reduced glutathione content while inhibiting lipid peroxidation. The results suggested that the antineoplastic activity of the A. catechu extract was related to its antioxidant activity.

In a third study, Monga et al. (2012) assessed the chemoprotective activity of A. catechu heartwood extract against DMBA-induced hepatocarcinogenesis in mice. The extract reduced the liver tumor incidence by 63.5%, and modulated the various antioxidant defense systems described earlier. The authors concluded that the catechin-rich extract exerts a chemoprotective effect by promoting the antioxidant defense system and inhibiting lipid peroxidation, and that these processes are linked to the modulation of transcription factor expression during hepatocarcinogenesis.

The conclusion from the three studies of Monga et al. (2011, 2012, 2013) is that an aqueous, catechin-rich heartwood extract of A. catechu exhibits potent anticancer activity as demonstrated by the prevention of squamous cell, mammary, and liver cancers in a dose-dependent manner.

ANTIMICROBIAL ACTIVITY

Burnett et al. (2007) tested a proprietary mixture of extracts of A. catechu and S. baicalensis for its ability to inhibit cyclooxygenase and 5-lipoxygenase enzyme activities in in vitro, cellular, and in vivo models. These two enzymes are important in the production of inflammatory cytokines from arachidonic acid. The results showed that this combination product was able to inhibit these two enzymes and reduce arachidonic acid-induced production of inflammation in a mouse ear-swelling model. No studies were conducted on A. catechu alone.

A subsequent study by these investigators (Tseng-Crank et al., 2010) assessed the anti-inflammatory activity of the proprietary S. baicalensis and A. catechu proprietary blend using lipopolysaccharide as the pro-inflammatory agent in animal and human immortalized cell lines and primary human cells. The combination product had a normalizing effect on the pro-inflammatory genes for cyclooxygenase, tumor necrosis factor, IL-1β, and IL-6 in all cell models. Furthermore, the central controlling factor for these genes, Nuclear factor - kappa B (NF-ƙB), was also downregulated. These results provide a mechanistic understanding of the anti-inflammatory effects of the combination product.

A 90-day oral safety study was conducted on a combination S. baicalensis and A. catechu product in male and female rats (Yimam et al., 2010). A dose of 1000 mg/kg/day was identified as the no-observed-adverse-effect level, and was the highest dose used in this study. No effects were observed with respect to body weight, feed consumption, clinical observations, organ weights, gross findings, spermatogenesis, estrus staging, ophthalmology, neurology, histopathology, or blood chemistries. These results indicate a very high level of safety.

In another study by Yimam et al. (2012), the analgesic activity of a proprietary S. baicalensis and A. catechu extract combination was assessed in rats and mice using paw edema, formalin test, and abdominal constriction assays. A dose of 100 mg/kg exhibited 58% and 72% inhibition of pain in the abdominal constriction and formalin tests, respectively, while 150 mg/kg reduced pain by about 40% in the paw edema assay. The analgesic effects were believed to be produced through the anti-inflammatory/antioxidant mechanism previously demonstrated.

In a subsequent study, Yimam et al. (2013) examined the efficacy of UP446, a combination of baicalin from S. baicalensis and (+)-catechin from the heartwood of A. catechu, in an experimental rat model of rheumatoid arthritis. A dose of 50 mg/kg of the combination product resulted in significant reductions in pain sensitivity, paw edema, and ankle diameter. With respect to mechanism, the product was shown to decrease the expression of the pro-inflammatory cytokines TNF-ƙ, IL-1β, and IL-6. As previously noted, the combination product is believed to act through the dual inhibition of cyclooxygenase and lipoxygenase.

ANTIMICROBIAL ACTIVITY

Various studies have examined the antimicrobial activity of A. catechu extracts, and demonstrated good-to-excellent activity depending on the organism involved. An aqueous extract of A. catechu exhibited moderate activity against a multiple drug resistant Salmonella typhi (Rani and Khullar, 2004). Patel et al. (2009) showed that an aqueous extract of A. catechu resin from heartwood exhibited excellent activity against Bacillus subtilis, while a petroleum ether extract gave excellent activity against Pseudomonas aeruginosa, and a chloroform extract was active against Staphylococcus aureus. No identification of active constituents was conducted.
An ethyl acetate extract of heartwood exhibited antimicrobial activity against *B. subtilis*, *S. aureus*, *Klebsiella pneumonia*, and *Shigella* species (Joshi et al., 2011). A methanol extract of *A. catechu* was shown to have antimicrobial activities against *B. subtilis*, *S. aureus*, *Sal. typhi*, *Escherichia coli*, *P. aeruginosa*, and *Candida albicans* (Negi and Dave, 2010). Aqueous and ethanol extracts of *A. catechu* demonstrated moderate activity against hospital isolates of methicillin-resistant *S. aureus* (Voravuthikunchai and Kitpipat, 2005). Lakshmi et al. (2011) have also demonstrated that ethanol extracts of *A. catechu* exhibit inhibitory activity against various microbes. Thus, various extracts of *A. catechu* heartwood exhibit antimicrobial activity, but in no case were the active chemical constituents for these activities identified.

**DISCUSSION**

The aqueous extract of *A. catechu* heartwood has been shown to be a rich source of catechin and epicatechin, with smaller amounts of flavonoids, chemicals with well-recognized antioxidant properties. Extraction with organic solvents as ethyl acetate, ethanol, methanol, hexane, and chloroform results in products with differing chemical compositions and subsequently differing physiological and pharmacological activities. The antioxidant properties of *A. catechu* heartwood extract has been demonstrated in a variety of *in vitro* systems and *in vivo* studies in rats, mice, and cell culture systems. The anti-inflammatory, antineoplastic, and analgesic activities are all believed to be due to the antioxidant activities, although no direct associations have been made.

Various studies involving catechin-rich and epicatechin-rich fractions from other plants have demonstrated antineoplastic (Chen and Zhang, 2007), analgesic (Kuang et al., 2010). A methanol extract of *A. catechu* demonstrated moderate activity against *S. baicalensis* and *A. catechu* at a dose of 250–500 mg/day for 1–12 weeks, with no adverse effects being reported (Yimam et al., 2010, 2012, 2013). It is not clear what per cent of the extract combination was provided by the *A. catechu*.

Several studies in animals and cell culture systems have also examined the anti-inflammatory and analgesic properties as well as the safety of the proprietary combination of *S. baicalensis* and *A. catechu* extracts (Burnett et al., 2007; Tseng-Crank et al., 2010). Although these results are very promising, the studies do not provide information on *A. catechu* alone and its relative contribution to the proprietary blend.

Finally, as previously noted, *A. catechu* heartwood extract is used as a component of betel quid. Oral cancer and epithelial dysplasia are known to be associated with the chewing of betel quid and are believed to be due to the production of reactive oxygen species and free radicals (Thomas and Kearsley, 1993; Nair et al., 2004; Waris and Nagi, 2014). Because of its antioxidant and free radical-scavenging ability, *A. catechu* heartwood extract may serve as a protectant and antineoplastic in betel quid. *Acacia catechu* extracts have been shown to exhibit antineoplastic and antiproliferative activities (Nadumane, 2011; Ghate et al., 2014).

**SUMMARY**

Various studies have shown that *A. catechu* heartwood is an excellent source of catechins and epicatechins as well as flavonoids, which have a high degree of antioxidant activity. The antioxidant activity has been well demonstrated by both *in vitro* and *in vivo* studies. The antioxidant activity is believed to be responsible for the anti-inflammatory, antineoplastic, tissue protective, and analgesic activities that have been demonstrated, and may be related to the antihypertensive and antidiarrheal effects. In spite of the long-term use of *A. catechu* and the general safety of catechins and epicatechins, there is a need for additional well-controlled safety studies in animals and humans. Additional well-controlled human efficacy studies are also needed. Furthermore, few studies have attempted to relate various effects to specific constituents.

**Conflict of Interest**

The authors have no conflicts of interest to report.
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