REVIEW ARTICLE

Received on:30/09/2017
Published on:18/01/2018

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CONFLICT OF INTEREST NONE DECLARED

Perspectives of Pinocembrin and its role as an emerging biomarker in future

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ABSTRACT

Background: Belonging to flavanone class, pinocembrin (5, 7-dihydroxyflavanone) is a flavonoid abundant in propolis. Pinocembrin was synthesized and approved by the State Food and Drug Administration of China for stroke clinical trials in 2008. In recent years, the biological and pharmacological effects of pinocembrin on systemic functions have attracted attention.

Objective: In this paper an overview is given of the biological mechanisms and the pharmacological evidence of pinocembrin on several biological functions.

Methodology: publication records as documented by the authors were reviewed for the study.

Results: The perspectives include antiinflammatory activity, as well as antifeedant, vasorelaxant, neuroprotective, antioxydant, antifungal, apoptosis-inducing activities. Its emerging role as a dominant biomarker for both biological materials has spread considerable interest.

Conclusion: It is cleared that due to its mechanisms, pinocembrin has many important applications in pharmacology and ethnobotany. All these areas that have been identified should form the focus of future researchers working on pinocembrin.

Keywords: biological activity; pharmacological activity

Introduction

Short historic overview

More than 250 population-based studies indicate that people who eat about five servings of fruit and vegetables a day have approximately half the risk of developing cancer of digestive and respiratory tract, comparing with those who eat fewer than two servings (Pamela et al, 2007; Foschiet al, 2010). Over 4000 structurally unique flavonoids have been identified in plant sources. They are found in fruits, nuts, flowers, seeds, herbs, vegetables, spices, stems, as well as tea and red wine. According to their substituents, they are usually subdivided into flavanones, flavanols, flavones, anthocyanidins and chalcones(Elliott et al, 2000).

The flavonoids display a variety of pharmacological activities of interest in the therapy or prevention of several diseases, including cancer, as cytotoxic, antiangiogenic, or antivascular agents (Touil YS, 2009). They have long been recognized to possess anti-inflammatory, antioxidant, antiallergic, hepatoprotective, antithrombotic, antiviral, and anticarcinogenic activities (Elliott Middleton et al, 2000). Most of the regulation of transcription by flavonoids appears to involve inhibition of phosphorylation signaling cascades or specific kinases. Studies have demonstrated that flavonoids inhibit activation of NF-κB in different cancer cell lines, suggesting a possible explanation for the inhibitory effects of these agents on cancer cells (Davis et al., 1999). Pinocembrin or 5, 7-dihydroxyflavanone, $C_{15}H_{12}O_4$, **Fig.1** is a flavanone that has been isolated from the seeds of Alpinia katsumadai Hayata (Huang et al, 2007). The plant grows wild mainly in Hainan, as well as Guangxi and Guangdong provinces in Southern China; it is recorded in the Chinese Pharmacopoeia as therapeutic drugs for the treatment of gastric disorders such as epigastric distension, nausea, vomiting and anorexia (Li et al, 2009). It has been extracted as a pure compound from propolis, and subsequently pinocembrin was synthesized and approved by the State Food and Drug Administration (SFDA) of China for stroke clinical trials in 2008 (Rui Liu et al, 2012). Belonging to flavanone class, it has also been isolated from the seeds of Alpinia katsumadai Hayata (Wang et al., 2010) and Alpinia galangal (Kumar et al, 2007), and identified as a major constituent of leaf resin of eastern cottonwood (Populusdeltoides) (Shain et al., 1982). Pinocembrin has long been recognized to have antioxidant, antibacterial and anti-inflammatory properties (Gao M et al, 2008b). Previous studies showed that pinocembrin reduced glutamate-induced SH-SY5Y cell injury and primary cultured cortical neuron damage in oxygen–glucose

deprivation/reoxygenation (OGD/R) (Gao et al., 2008a), alleviated cerebral ischemic injury in the middle cerebral artery occlusion rats (Gao et al., 2008b,), and improved cognition by protecting cerebral mitochondria structure and function against chronic cerebral hypoperfusion in rats (Guang et al, 2006). Rui Liu et al, (2012) suggested that pinocembrin has potential therapeutic effects for cognitive impairment; it alleviated learning and memory deficits in a vascular dementia rat model through mitochondrial protection. Like many other flavonoids, pinocembrin has been shown to relax the contraction evoked by KCl in rat thoracic aortic rings in a concentration-dependent manner (Calderone et al., 2004). Among the components of propolis, pinocembrin is one of flavonoids drawing much attention because of its benefits on human health due to anti-inflammatory, antioxidant, anti-thrombotic, antimicrobial, anti-allergic, hepatoprotective, anti-viral, cancer chemopreventive, and anti-asthmatic activities (Guang HM et al, 2006).

Aim and scope of this review

Only recently, the effects of pinocembrin on systemic functions have attracted attention. This novel approach could lead to new perspectives for its use as a pharmacological agent. In this paper an overview is given of the biological mechanisms and the pharmacological evidence of pinocembrin on several biological functions. These include antiinflammatory activity, as well as antifeedant, vasorelaxant, neuroprotective, antioxydant, antifungal, apoptosis-inducing activities. Even though we have attempted to cover many different pharmacological actions, we are aware that there have been several omissions for some effects of pinocembrin. Further studies and exploration are required in these areas. Nevertheless, it is our opinion that the most influential articles using multiple search terms and manuscript sources have been included in the present review. This may be an important way for health care professionals and researches to keep abreast of current trends.

History

Pinocembrin is found in high amounts in the rhizomes of fingerroot (Boesenbergia pandurata) or "Kra-chai" in Thai (Punvittayagul et al, 2011). Pinocembrin has been extracted as a pure compound from propolis. History informs us that the famous queen of ancient Egypt, Cleopatra, used a mixture of fresh milk and honey in her bath. The legendary queen of the Nile, the mistress of Louis XV and the Chinese empresses maintained their skin healthy and shiny owing to the skin-enhancing qualities of honey (www.Chefs-help.co.uk).

Sources of pinocembrin

As shown in (**Fig. 1**), pinocembrin has been isolated from a variety of plant parts in diverse flora, such as Heartwood of Pinus, leaves of Eucalyptus, aerial positions of two genera of the compositae, bud resin, leaf resin of Populus (Liu R et al, 2012).

Isolation and identification:

Houghton et al., 1995 have determined pinocembrin content in propolis using different types of chromatographic techniques such as densitometry and high performance liquid chromatography. As results they found that the pinocembrin content of samples of proprolis from different geographic areas was found in the range 4.0 to 4.6% w/w (**Fig 2**).

Chemical structure

Pinocembrin (**Figure 3**) has been extracted as a pure compound from propolis, and subsequently pinocembrin was synthesized and approved by the State Food and Drug Administration (SFDA) of China for stroke clinical trials in 2008.

Biological and pharmacological properties

Toxicity

Using MTT assay for testing cell viability, we demonstrated that pinocembrin (from 100 to 300 μg/ml) had no cytotoxic effect on RAW 264.7 cells (Soromou et al, 2012) or male rats (Charoensin et al., 2010).

Antimutagenic activity

Pinocembrin exhibited a strong antimutagenic activity against mutagenic heterocyclic amines. They demonstrated that this effect was due to the inhibition of the first step of enzymatic activation of heterocyclic amines (Trakoontivakorn et al., 2001). Krizkováet al, 1998 studied the effect of flavonoids on ofloxacin-induced mutagenicity in Euglena gracilis. As results, they showed that pinocembrin possesses considerable antimutagenic properties against ofloxacin-induced bleaching of E. gracilis.

Antioxidant activity

Oxidation is one of the most important mechanisms responsible for the major degenerative diseases of aging, including cancer, heart disease, cataracts, and cognitive dysfunction. Evidence from intervention studies indicates that antioxidants may prevent many of the oxidative processes that contribute to the causation of these chronic diseases (Daayf F et al. 2008). Pinocembrin exhibited cardioprotective effects

during I/R, evidenced by improved cardiac function, fewer arrhythmias, and smaller infarcts in treated hearts. These outcomes may be due to pinocembrin's antiapoptotic and anti-oxidative stress effects and its ability to increase the phosphorylation of Cx43 in ischemic myocardium (Lungkaphin et al, 2015). Pinocembrin is unique to honey and found in the highest amount relative to other antioxidants. Darker honeys and those high in water content have stronger antioxidant potential (www.Chefs-help.co.uk).

Anti-inflammatory activity

The in vitro and in vivo effects provided by pinocembrin against lipopolysaccharide-induced inflammatory responses were investigated. The authors concluded that pretreatment with pinocembrin remarkably regulated the production of TNF-α, IL-1β, IL-6 and IL-10 via inhibiting the phosphorylation of IκBα, ERK1/2, JNK and p38MAPK. The in vivo model proved that pinocembrin attenuated the development of pulmonary edema, histological severities, as well as neutrophil, macrophage and lymphocyte infiltration (Soromou et al, 2012). Brain microvascular endothelial cells (hBMECs), indispensable to the creation and maintenance of brain homeostasis are the early targets of various toxic molecules, such as amyloid-β peptides and reactive oxygen species. In Alzheimer's-related deficits, pinocembrin may serve as a therapeutic agent for BMEC protection. The cytotoxicity induced in hBMECs can be rescued by pinocembrin treatment. This mechanisms may be associated with the inhibition of inflammatory responses, involving reduction of the release of pro inflammatory cytokines, down regulation of phosphor-IKK level, inhibition of MAPK activation, relief of IκBα degradation and blockage of NF-κB p65 nuclear translocation (Liu R et al, 2014).

Pinocembrin as survival enhancer (apoptosis)

Pinocembrin may prove to be an important candidate for treating cognitive manifestations of Alzheimer's disease. It is known that amyloid-β peptide plays a pivotal role in the pathogenesis of Alzheimer's disease. Interaction between amyloid-β and the receptor for advanced glycation end products has been implicated in neuronal degeneration associated with the disease (Rui Liu et al, 2012). In contrast, pinocembrin is known to regulate mitochondrion-mediated apoptosis by restoration of B cell lymphoma 2 (Bcl-2) and cytochrome c and inactivation of caspase 3 and caspase 9 (Sung et al, 2009; Rui Liu et al, 2012). Pinocembrin is also illustrated to modulate apoptosis synergistically with the inactivation of SAPK/JNK-c-Jun pathway (Rui Liu et al., 2012) and induced apoptosis of LNCaP cells and arrested cell cycle at S and G2/M phase and involved in the dissipation of mitochondrial membrane potential (Chen et al, 2013).

The research conducted by Liu R et al., 2012 showed that pinocembrin inhibits the up regulation of RAGE transcripts and protein expression both in vivo and in vitro, and depresses the activation of p38MAPK- MK2-HSP27 and SAPK/JNK-c-Jun pathways and the downstream NF-kappaB inflammatory response subsequent to Abeta-RAGE interaction. The mitochondrial dysfunction is also alleviated by pinocembrin through improving mitochondrial membrane potential and inhibiting mitochondrial oxidative stress. Therefore pinocembrin regulated mitochondrion-mediated apoptosis by restoration of bcl-2 and cytochrome c and inactivation of caspase-3 and caspace-9.

Antifungal activity

Mycotic infection of the scalp, tinea capitis, is a common disease in developing countries. The use of medicinal herbs in the treatment of skin diseases is a useful practice in many parts of the world (Ali-Shtayeh et al, 1986; Irobi et al, 1993). Pinocembrin is a promising bioactive compound for treatment of P. italicum infections on postharvest citrus fruit. It is a strong antifungal agent against P. italicum. The respiration rates of P. italicum during spore germination and mitochondria in state 2 and state 3 from mycelia are inhibited when exposure to pinocembrin. At the end of their studies, the authors proved that pinocembrin inhibits the mycelial growth of P. italicum by interfering energy homeostasis and cell membrane damage of the pathogen (Peng et al., 2012). In addition, the purpose of the investigation conducted by Shain and Miller (1982) was to determine if inhibitory substance(s) occur on cottonwood leaves and, if so, their identity, origin, and potential significance in disease resistance. Their results showed that a sufficient amount of pinocembrin is present on the surface of young, expanding leaves to contribute substantially to their resisitance to M. medusa and to a lesser degree to M. brunnea.

Anti-irritant activity

Irritant contact dermatitis is a non-immunologic and non-specific inflammatory disorder of the skin that is accompanied by disruption of the barrier and dehydration of the uppermost layer of the skin. Hence, agents contributing to skin hydration and the maintenance of its homeostasis are required (Tan et al,

2014; Andersen et al, 2007). Honey also acts as an anti-irritant, making it suitable for sensitive skin and baby care products. If pure honey is used in combination with olive oil it can be quite effective in the treatment of minor wounds. It was reported that manufacturers have used honey in everything from hand lotions and moisturizers to bar soaps and bubble baths. Honey is humectants, which means that it attracts and retains moisture. This makes honey a natural fit for a variety of moisturizing products including cleaners, creams, shampoos and conditioners (www.Chefs-help.co.uk).

Antimicrobial activity

Peng et al. (2012) showed that the antimicrobial activity of propolis is attributed to phenolic components, especially flavonoids. As an important flavonoid in propolis, the compound demonstrated strong antimicrobial activities against bacteria including Bacillus subtilis, Staphylococcus aureus, and fungi such as Candida albicans, Aspergillus niger, Fusarium spp., Rhodotorula glutinis, Microsporum gypseum, Trichophyton mentagrophytes, and Trichophyton rubrum.

Pinocembrin was screened for antimicrobial activity against Neisseria gonorrhoeae and the findings showed that the natural product inhibits 100% of the Neisseria gonorrhoeae panel (Ruddock et al, 2011). The demand for propolis is increasing due to its health benefits and use in cosmetic and food products. High concentrations of pinocembrin are found in propolis which has a strong antimicrobial activity against Gram-positive bacteria and yeast (Uzel et al, 2005).

Anticancer activity

Nowadays, many dietary phytochemicals can be considered as chemopreventive agents because they have been shown to inhibit carcinogenesis. The mechanism of chemical protection against the initiation stage involves the induction of phase I and phase II xenobiotic-metabolizing enzymes. Moreover, the chemopreventive activity also influences cell proliferation, differentiation and apoptosis, preventing the accumulation of damaged cells. Pinocembrin increases the number of GST-P positive foci higher compared to control when administered before diethylnitrosamine injection. High doses of pinocembrin promote the development of preneoplastic lesions in the rat livers. Its administration before diethylnitrosamine injection induces lipid peroxidation. This is one result supporting the suggestion that the promoting effect of pinocembrin might be due to lipid peroxidation (Charatda Punvittayagul et al., 2012).

Neuroprotective activity

Pinocembrin has neuroprotective effects on ischemic and vascular dementia animal models. Oral administration of pinocembrin improved cognitive function, preserved ultrastructural neurophils and decreased neuro degeneration of cerebral cortex in Abeta25-35-treated mice (Liu R et al., 2012).

Anti-schemic stroke activity

Ischemic stroke has become an increasingly severe medical and social problem with high attach and fatality rate, due to rapid growth of aging people populations. It is promising that pinocembrin could be developed as a new drug to treat ischemic stroke (Yang et al., 2012).

The aim of the present study conducted by Meng et al, 2014 was to investigate the effect of pinocembrin on cognitive ability impairment in a rat model of transient global cerebral ischemia. Pinocembrin treatment was found to alleviate the cognitive impairments, decrease the neurological scores, reduce the number of GFAP-positive cells and diminish neuronal loss. Therefore, pinocembrin alleviated memory impairment in transient global cerebral ischemia.

Anti-allergic activity

The development of this allergy is a biphasic reaction, comprising an early and a late phase. Type I allergy is induced by certain types of antigens such as from foods, dust mites, medicines, cosmetics, mold spores, and pollen. This class of antigen induces the production of antigen-specific IgE antibodies that bind to receptors on mast cells or basophils. The early phase reaction or type I allergy occurs within minutes when the sensor cells are activated to produce the mediators (histamine, serotonin) that are released from the cell. The mediators induce broncho constriction, vasodilation and mucous secretion (Matsuda et al., 2004). Pinocembrin inhibits histidine decarboxylase activity and histamine, and mitigated the damage in the mitochondrial membrane, formation of cytoplasmic granules and degranulation. The findings validated that Pinocembrin, as a potential histidine decarboxylase inhibitor, provides evidences and is a new candidate for natural anti-allergic drugs (Hanieh et al, 2017).

Pinocembrin as biomarker

Adelmann et al., (2006) have reported that since color enhancement after Al^{3+} complexation applies just for more hydroxylated flavonoids, the alternative

techniques herein applied were of value for pinocembrin detection and estimation. They concluded that GC–MS, CZE with alkaline buffer, and TLC/densitometry all them provided good resolution to distinguish and to quantities this specific flavonoid as a dominant biomarker for both biological materials.

Conclusion and Future trends

From the above data it is cleared that due to its mechanisms, pinocembrin has many important applications in pharmacology and ethnobotany (figure 4). Previous works have reported that these biological and pharmacological effects of pinocembrin on systemic functions have attracted attention. Although the biological mechanisms and the pharmacological evidence are known, there are possibilities that other useful and important knowledge might also be elucidated if studies consider the above mentioned factors .All these areas that have been identified should form the focus of future researchers working on pinocembrin.

Acknowledgement

The authors are grateful to Dr Mohamed KEYRA and Pr Youssouf SIDIME of the Department of Veterinary Medicine, Institute of Sciences and Veterinary Medicine (ISSMV)/Dalaba, Republic of Guinea for their assistance.

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Cite this article as:

Dr. Lanan Wassy Soromou ; Perspectives of Pinocembrin and its role as an emerging biomarker in future. Asian Journal of Pharmacology and Toxicology 05 (18); 2018; 16-23.

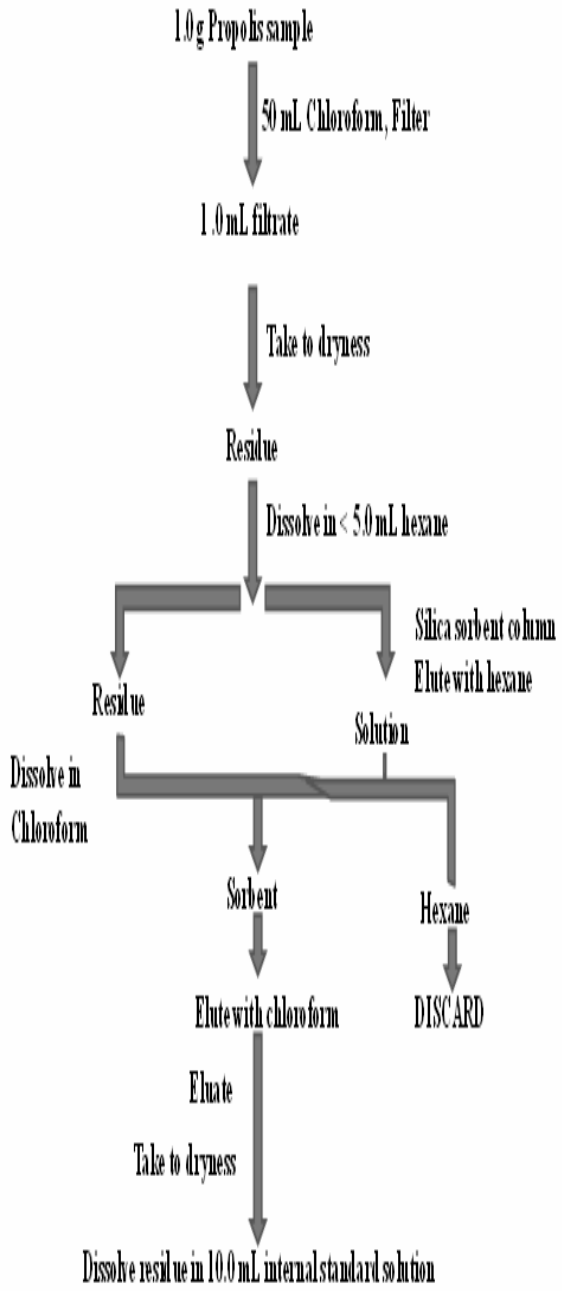

Figure-2 Isolation and identification of pinocembrin (Houghton et al., 1995)"

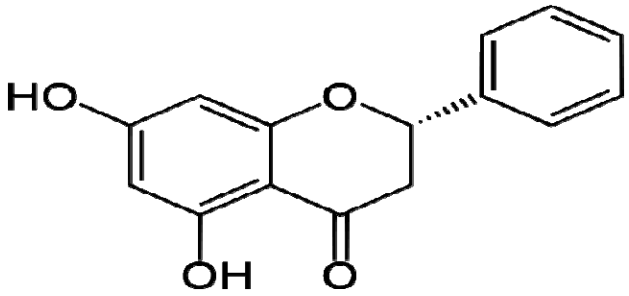

Figure 3-Chemical structure of Pinocembrin

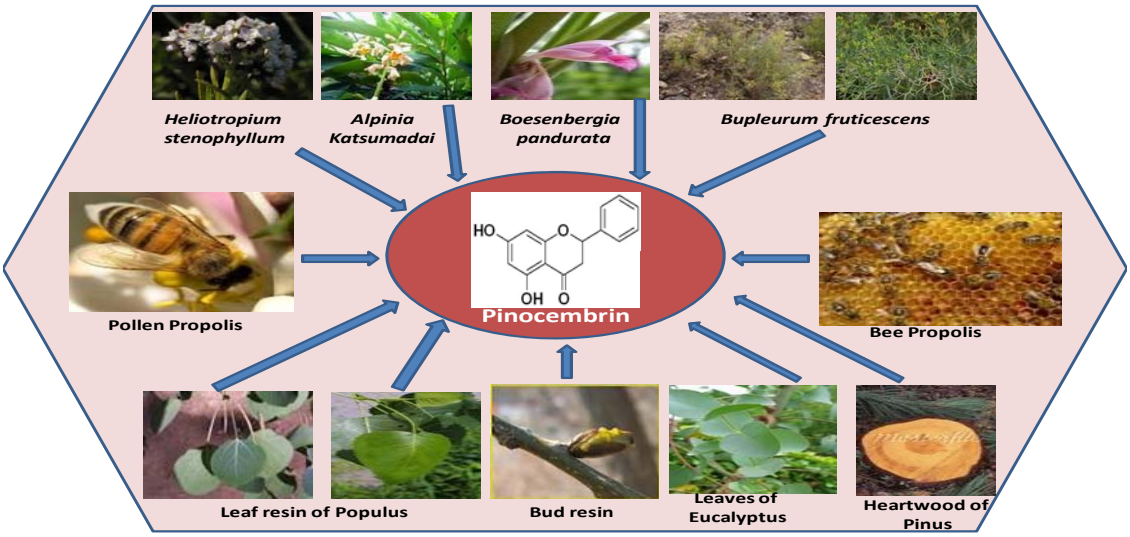

Figure 1- Sources of pinocembrin

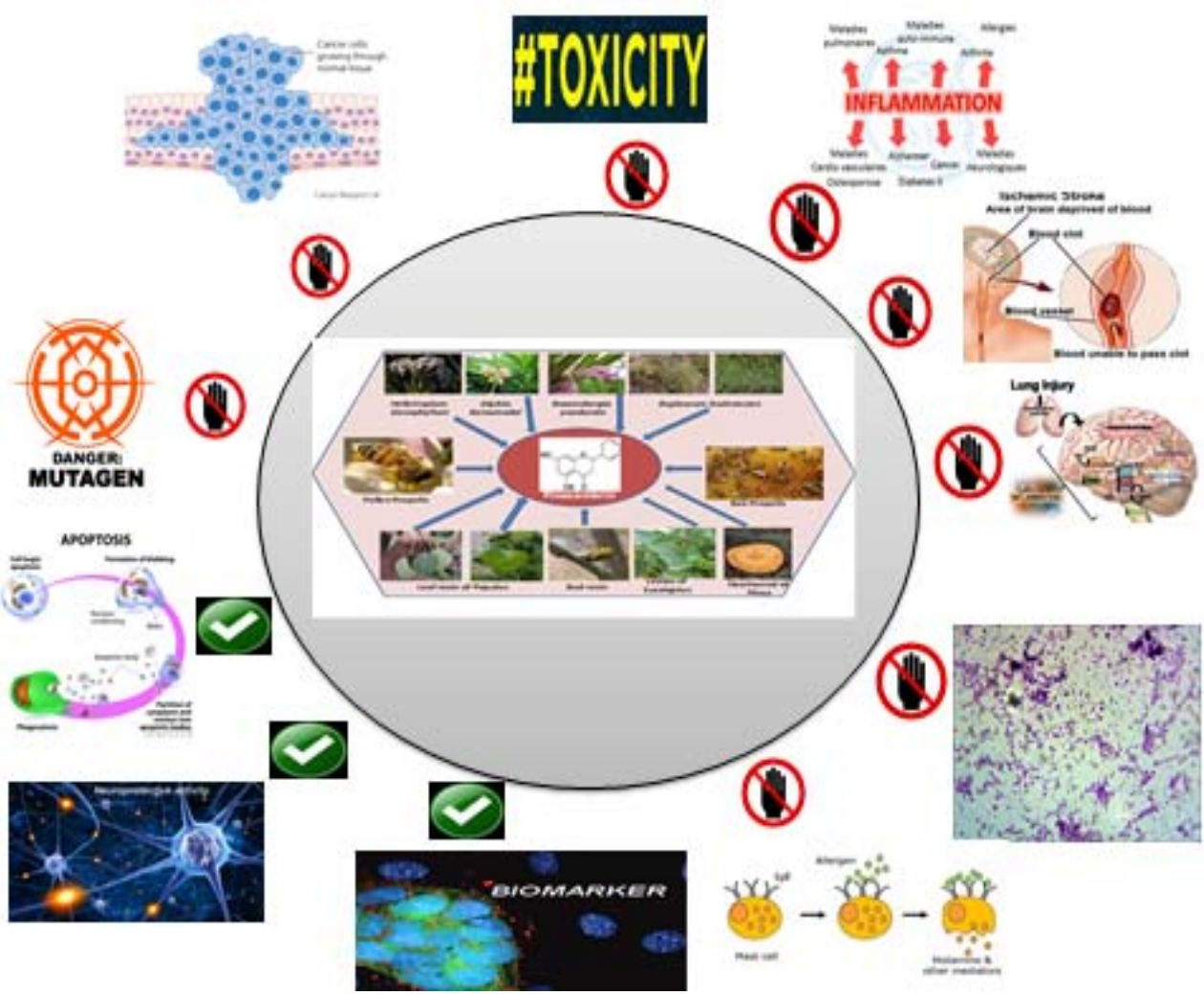

Figure 4 –Toxicity of pinocembrin