

A Critical review on ‘Marking nut’— *Semecarpus anacardium* Linn.

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Abstract: Secondary metabolites and related phytochemicals are used as therapeutics in the pharmaceutical industry. These therapeutics are useful in treating various ailments such as cancer, inflammation, diabetes, neurological disorders, cardiovascular diseases. The phytochemicals present in *Semecarpus anacardium* Linn. are well-recognized for their medicinal abilities. The phytoconstituents— Bioflavonoid's, Phenols, Bihlavanols, present in the plant extracts, cure several ailments including psychological disorders as well. Thus, triggering a detailed investigation in the healing properties of these compounds. This article focuses on the critical review of the anti-cancerous, anti-inflammatory, neuroprotective effects and psychological effects of *Semecarpus anacardium* plant extracts. Further the possible future perspectives in using different *Semecarpus anacardium* nut extracts as remedies are also discussed in detail.

Keywords: *Semecarpus anacardium*, anti-cancer, anti-inflammatory, neuroprotective effects.

Introduction:

Several secondary metabolites and naturally occurring chemical substances produced by microbes, plants and animals have important medicinal properties (Balandrin et al., 1985; Costa-Neto, 2005; Gupta, 2014). These are being used as folk medicines since time immemorial for the treatment of various ailments (Jain & Sharma, 2013). Some Well-known bioactive chemicals used as drugs are Morphine, Caffeine, Salicylic acid, Digoxin and many more (Orhan, 2014). These bioactive chemicals are obtained from different plant parts such as the roots, stem, leaves, fruits; and prescribed as medicine in ‘Ayurveda’ and ‘Homeopathy (Gromova, 2013). Usually, plant parts are collected and processed by various methods, until the extract contains the desired active ingredient which is used as medicine (Akbar, 2020). We have evolved with these medicinal plants, therefore our cells possess receptors for these phytochemicals (Elphick & Egertová, 2001). Responses of our cells to these natural compounds are crucial in drug discovery (Orhan, 2014) (Linn et al., 2020). Therefore many of these phytochemicals are in use for treatment various serious diseases like cancer, cardiovascular diseases, pulmonary disorders, other physiological disorders and psychological disorders (Jain & Sharma, 2013) (Gibson, 1968).

Vast amount of literature has been recorded over the past decades that describes the intense medicinal nature of the bioactive compounds derived from various plants (Upreti et al., 2016). One such well-studied genus is *Anacardium*, belonging to the family Anacardiaceae. (Semalaty et al., 2010).



Semecarpus anacardium (SA)

Semecarpus anacardium is commonly known as 'Marking nut'. This nut is heart shaped; while the tree is natively found in Sub-Himalayan region, Assam (Khasia hills), Madhya Pradesh, Gujarat, Konkan region (Maharashtra), Kanara forest (Tamil Nadu) and Northern Australia (Upreti et al., 2016). The nut extracts are known to possess therapeutic compounds. These compounds (Bioflavonoid's, Phenols, Bihlavanols, Anacardic acid and others) provide curating effects; when consumed in proper amount and concentration (Premalatha, 2000). The corrosive resinous juice present between the shell and the kernel of the fruit has a pale milky colour when fresh. This layer turns ‘Black’ when exposed to air and is used in the Homeopathic preparations of mother tincture (Gibson, 1968).

The phytoconstituents of this nut include phenols and catechol's that demonstrate medicinal effects e.g. Bihlavanol A, Bihlavanol B and anacardoside. These phytoextracts are used against ailments such as skin disorders, rheumatoid arthritis, constipation, intestinal infections, diabetes, tumour's and cancers in different regions (Plant, 2012; S.H, 2008). A table containing isolated and identified bioactive compounds of *Semecarpus anacardium* is given below:

Biflavonoids	Phenolic compounds	Other compounds
Biflavone-A, C, A1, A2, Tetrahydrorobustaflavone, tetrahydroamentoflavone Jeediflavanone, Semecarpuf flavanone, Galluf flavanone, Anacardoflavanone, Nallaflavanone, Semicarpetin, Anacarduf flavanone, o-trimethyl bioflavanone A1, o-trimethyl bioflavanone A2, o-tetramethyl bioflavanone A1, o-hexamethyl bichalcone A, o-dimethyl biflavanone B, o-heptamethyl bichalcone B1, o-hexamethyl bichalcone B2, o-tetramethyl biflavanone C	Bhilawanols (Monoenepentadecyl catechol I) Bhilavanol B (Dienepentadecyl catechol II) Semecarpol, Anacardol	A Anacardic acid, Cardol, Catechol, Alkenyl catechols, Semecarpetin, Anacardol, Anacardoside, Semecarpol, Monolefin I, Diolefin II, Oleic acid, Linoleic acid, Palmitic acid, Stearic acid, Arachidic acid

Table 1: The table lists the known bioactive components extracted from *Semecarpus anacardium* nut

Out of the many phytopharmacological studies carried out in the past, we have assorted and reviewed crucial properties of this remarkable 'Nut'. Present review is focused on the diverse effects of the phytoextracts from *Semecarpus anacardium* nut on cancer, inflammation, neuroprotection, psychology and other physiological disorders.

Anticancer activity:

Semecarpus anacardium milk extract showed anti-cancerous along with hepatoprotective activities in hepatocellular carcinoma rats. The bioactive compounds from the nut have yielded promising results in treating urinary bladder, liver cancer and leukaemia. Upon treatment with nut extract there was recorded a marked reduction of α -fetoprotein level (Hepato-cellular carcinoma marker) in histopathological analysis (Premalatha & Sachdanandam, 1999). However, these findings are unconfirmed by more sensitive techniques like immunoblotting and ELISA. Simultaneously it is yet unclear that which individual bioactive component in the nut extract is responsible for the reduction of Alpha-Fetoprotein (AFP). The AFP has three glycoforms i.e. AFP-L1, AFP-L2 and AFP-L3 (Singhal et al., 2012). A detailed investigation can be carried out to find which specific bioactive component is responsible for reducing the level of a specific AFP glycoforms. Relying only on AFP as a marker can be insufficient as it is undetected in the early stages of Hepato-cellular carcinoma (HCC) condition. Therefore, one can use other known HCC markers for prognosis such as Heat-shock protein-27 (HSP27), HSP70, Glypican-3 (GPC3), Squamous cell carcinoma antigen (SCCA), Golgi protein 73 (GP73), Tumour-associated glycoprotein 72 (TAG-72) and Zinc- α -2-glycoprotein (ZAG). Furthermore, effects of *S. anacardium* extracts can be examined on enzymatic markers of HCC such as Des- γ -carboxyprothrombin (DCP), γ -glutamyl transferase (GGT) and α -L-fucosidase (AFU); in addition to HCC associated cytokines such as transforming growth factor- β 1 (TGF- β 1) and vascular endothelial growth factor (VEGF). Assessment of effect of bioactive compounds in the nut extract on gene expression needs to be analysed by measuring the mRNA levels of AFP and MiR-500 (miRNA) (Tateishi et al., 2012). We speculate that the results of these findings will aid in confirming the anti-HCC role of *S. anacardium* extract.

In a study it has been shown that *S. anacardium* milk extract stimulated apoptotic signals in cancerous cell lines, inhibited DNA synthesis (dose-dependent) and induced NOS expression (time-dependent) and thereby inhibited the growth of T47D human breast cancer cell lines. Furthermore, *S. anacardium* -milk extract treatment can alter the gene expression of the apoptotic key proteins; such as *bcl2*, *bax*, cytochrome 'C' and Poly (ADP-ribose) polymerase (*PARP*) (Mathivadhani et al., 2007). This added further evidence to the anti-cancerous properties of *S. anacardium*. Although the study postulated the role of unidentified flavonoids from *S. anacardium* having anti-cancerous activity. Additional investigation in this aspect might help us gain a better grasp on the baseline mechanism behind the anti-cancerous properties of 'Marking Nut'.

One of the core components present in *S. anacardium* nut is catechol. The catechol and its derivatives (I–IV) showed anti-cancerous properties when used on human cancer cell lines. Researchers extracted a bioactive component 3-(8'(Z),11'(Z)-pentadecadienyl) catechol (*S. anacardium* -3C) from *S. anacardium* methanolic extracts. They proved that *S. anacardium* -3C damages the tumour cell lines and inhibit cell cycle; when combined with 'Doxorubicin' (widely used synthetic anti-breast cancer drug). The effect of SA-3C against multidrug resistant tumour cells was also noticed (Nair et al., 2009). Altogether from these studies we can derive that there are many unexplored therapeutic aspects of SA nut extract. In future one can focus on the effect of SA-3C on *BRCA1* (Semmler et al., 2019), and other fatal cancer types such as Leukaemia, Lung, Colon cancer. Additional studies can aim to inquire on the synergistic drug action with Chloroquine, Abemaciclib, Palbociclib, Ribociclib, Olaparib, Talazoparib as well (Maycotte et al., 2012; Waks & Winer, 2019). On a similar scale, comparative synergistic interactions with other reported phytochemicals in treating breast cancer can be carried out. Such data can enable us to have a wider and better understanding regarding SA-3C drug action. A combinatorial drug study could be conducted to assess the combined action of *Semecarpus anacardium* extracts with *Bacopa monnieri* extracts; along with their respective phytochemicals (Mallick et al., 2015).

Anti-inflammatory activity:

Inflammation is defined as the body's innate response against foreign pathogens or foreign component (Halliwell et al., 1988). When immune cells such as monocytes and neutrophils carry out phagocytosis, they release free radicals. Flavonoids scavenge these free radicals, leading to low peroxide levels at the site of inflammation, the reason why these are classified as anti-inflammatory and antioxidant agent (Antonio Ayala, Mario F. Muñoz, 2014; Ramprasath et al., 2005).

Paw edema in rats is a classical model used for inflammation related studies. Paw edema in Wistar rats is developed in two phases. The first phase initiated by histamine and serotonin; while the second phase by the release of COX. From this basis, a study showed that SA milk extract might have inhibited histamine, serotonin and COX. This also lead to inhibition of fibroblast proliferation and monocyte invasion (Ramprasath et al., 2004). Cyclo-oxygenase is also known to participate in innate responses such as allergic reactions, inflammation and platelet aggregation. These innate responses are inhibited by (NSAIDs)(Halliwell et al., 1988). A study conducted by Ramprasath and colleagues proved the anti-inflammatory and anti-pyretic effects by SA milk extract dose in Wistar albino rats. The behaviour of SA extracts was similar to NSAIDs(Ramprasath et al., 2006). The observation has opened a new possibility in developing SA compounds as an Anti-pyretic therapeutic drug in the future.

The phenolic compounds present in SA such as semicarpol, bhillawanol and flavonoids are known to cure Rheumatoid arthritis in many model organisms (Semalty et al., 2010). The ethyl acetate extract of *Semecarpus anacardium* is known to show anti-inflammatory activity against carrageenan induced rat paw edema (Selvam et al., 2004). SA - milk concoction is a widely investigated type of extract. In paw edema in Albino Wistar rats SA milk extract treatment reduced the myeloperoxidase, nitric oxide and TNF- α levels in these rats, proving the anti-inflammatory activity against acute and chronic cases of paw edema present in SA-milk concoction (Ramprasath et al., 2006).

Arthritic and paw edema induced male Wistar rats contain low levels of antioxidant enzyme levels. Upon treatment with SA, these rats showed prominent improvement in their condition and marked elevation of Catalase (CAT), Glutathione (GSH), Glutathione peroxidase (GPx), Lipid peroxides (LPO) and Superoxide dismutase (SOD) in the Spleen and Thymus of these rats (Ramprasath et al., 2005). This reduced the inflammation in rats as the upregulation of these enzymes are known marker for anti-oxidant activity.

The effects of SA-Water extract on antioxidant activity was carried on Lymphoma induced AKR mice strain (Cancer model strain). The levels of CAT, SOD, Glutathione transferase and Lactate dehydrogenase were elevated and improvement in mice liver (Verma & Vinayak, 2009). This investigation further proved that SA-water concoction is more potent in treating Lymphoma as compared to Doxorubicin.

Osteoarthritis characterized by severe knee cartilaginous destruction and inflammation has affected more than 150 million people over the world. Thus, developing therapeutics for osteo-arthritis can pave a new path in the pharmacological field (Wang et al., 2020; Zhao et al., 2020). A detailed investigation, is required to identify the free radical reducing flavonoids present in the SA extract. It will be helpful in generating synthetic analogs as anti-

inflammatory therapeutics. Pharmacophore based studies, molecular docking, inhibition examinations like methods can be used to determine the underlying activities of *S. anacardium* phytochemicals (Chopade et al., 2015; Emran et al., 2015). This will gift us a clear understanding about the precise working mechanism of the SA extracts in treating inflammation.

Neuroprotective effects:

The brain and central nervous system together form the most crucial and complex network in the body respectively. Their combinatorial actions control the most vital processes in the body. Since decades, scientist have been studying and understanding the complexities behind their working (Bunge & Wright, 2007). One of the aspects, that requires deeper investigation is 'neuro-degeneration' that occurs as the age progresses. It leads to cognitive defects, memory loss, improper degradation of proteins, behavioural disorders, apoptosis and overall damage in the brain's neuronal network (Gitler et al., 2017; Pugazhenthil et al., 2011); thus, rendering the body dysfunctional and mentally crumbled. Other neurodegenerative disorders, those more dangerous and life threatening, are Spinocerebellar ataxias (SCAs), Dementia with Lewy bodies (LBD), Frontotemporal dementia (FTD), Amyotrophic lateral sclerosis (ALS); Huntington's disease (HD), Parkinson's disease (PD) and Alzheimer's disease (AD) (De Jager et al., 2018; Gan et al., 2018). All these neurodegenerative disorders affect the sensory-motor neurons and phenotypic neuronal plasticity of the brain (Frank et al., 2013).

Numerous therapeutics targeting deleterious effects of neurodegeneration have been developed over the past few decades. Some phytochemical containing drugs have shown neuroprotective effects on a molecular, genetic, hormonal, immunological, and proteomic level (Mohd Sairazi & Sirajudeen, 2020). SA inhibits the Acetylcholinesterase enzyme activity. This action of SA decreases the breakdown rate of Acetylcholine and thereby enhancing significant improvement in cognitive processes and amelioration of memory defects (Vinutha et al., 2007).

A study in 2012 found two Catechol alkenyl's possessing neuroprotective properties in dichloromethane extract of SA; using High Performance Liquid Chromatography, mass and NMR spectrometry. They were named as 1',2'-dihydroxy-3'-pentadec-8-enylbenzene and 1',2'-dihydroxy-3'-pentadeca-8,11-dienylbenzene. Both the phytochemicals demonstrated inhibitory activity against Acetylcholinesterase and butyryl cholinesterase. In addition, they used genetic algorithm and generated various docking sites possible for these compounds. The overall results helped in confirming the docking and interaction of 1',2'-dihydroxy-3'-pentadec-8-enylbenzene and 1',2'-dihydroxy-3'-pentadeca-8,11-dienylbenzene with Acetylcholinesterase (Adhami et al., 2012). The study yielded a detailed molecular level confirmation, that bioactive components present in SA extracts have curing properties.

In a comparative study conducted between Chloroform-ethanol Soxhlet *Semecarpus anacardium* extract and hydrochloric *Withania somnifera* extract. The electron microscope images physically proved that SA extract provided protection from neuronal damage by 80% as compared to *Withania somnifera* extract (Shukla et al., 2000)(Waks et al., 2015). This study opened an additional door for future studies involving the uses of *Semecarpus anacardium* as a 'neuroprotective drug'.

Psychological effects:

The field of alternate medicines have made the most of this wonder 'Nut'. The homeopathic medicinal guide, commonly known as 'Materia Medica' has been using the therapeutic outputs for over 200 years (Gibson, 1968). The appropriate dose is commonly used by Homeopathy practitioners to treat patients with neurological defects. These patients also suffer from disturbed gastric juices secretions, eczema, irregular bowel movements; apart from memory loss commonly observed in them. The patients seldom complain about mental fatigue, recurring headaches and blurred vision. Therefore, such patients are treated using alcoholic extract of the marking nut (Gibson, 1968). Much of the required documentary evidence is yet to come along in using the Homeopathic dilutions for treating physiological distress among patients.

Other significant effects:

Anti-oxidant activity has been demonstrated SA milk extract mediated steady decline in the reactive oxygen species (ROS) and nitrogen species along with the mitochondrial membranal potential (Jaya et al., 2010). Male albino rats treated with SA-milk concoction showed altered carbohydrate metabolism and energy production. The

Phosphoinositide 3-kinases and Protein kinase B / AKT enzymes levels were upregulated in the skeletal muscles of these rats; upon administration of SA milk extract (Panchanadham et al., 2011).

Immune stimulant properties of SA-catechol derivatives I and IV has been observed as it increases WBC count in Wistar albino rat models. Additionally, it also elevated the HDL cholesterol, decreased LDL and lipid profile in plasma and tissue of these rats. The SA treatment helped boost cardiovascular endurance in these rat models (Sundaram et al., 2018). As these conditions are linked towards LDL deposition, reduced HDL levels and stress (Mundi et al., 2018; Gofman et al., 2019). The use of catechol and its derivatives (I-IV) might have different therapeutic advantages in other tissues of the body. These salient features might ameliorate other such physiological distress by controlling cardiovascular dysfunctions, thereby preventing the risk of heart failure, cardiac arrest, hypertension, and peripheral heart diseases.

Chloroform and petroleum ether SA nut extracts have shown anthelmintic activity as compared to ethanol and water extracts (Pal et al., 2008). *S. anacardium* n-butanol seed extract has demonstrated significant anti-bacterial activity attributed to its prime chemical 'Acyclic isoprenoid' (Purushothaman et al., 2017). We can further explore these properties in developing therapeutics against severe intestinal infections in humans.

Other parts of the *Semecarpus anacardium* have also been successfully implicated in anti-cancerous and anti-oxidant activities. Like nut extract, SA leaf extract also had similar anti-cancerous activity against breast cancer cell lines (Singh et al., 2018). However precise identity of biochemical responsible for this activity is yet to be identified. In contrast SA stem bark ethyl acetate extract contains the essential component that generates anti-inflammatory activity in-vitro, were identified as 'Butein' (3,4,2',4'-tetrahydroxychalcone) and 7,3',4'- trihydroxy flavone, These compounds also inhibited COX-1 (Selvam et al., 2004). However, the in-vivo mechanism by which these compounds bring about relief from inflammation is yet to be studied.

Conclusion and Future direction:

In recent past has witnessed a surge in the usage of herbal products as therapeutic drugs. Several pharmaceutical companies have invested capitals in plant-component derived drugs mainly due to their therapeutic effects on multiple target organs, instead of single organ. From the available literature it is evident that, *Semecarpus anacardium* is a potential candidate to be recognized as a 'Herbal Drug'. The phytochemicals in SA have proved to possess potential as Anti-cancerous, Anti-inflammatory, Neuroprotective, antihelminthic and antibacterial therapeutics. The bioactive compounds in the nut also showed significant positive changes at the physiological, neuronal, behavioural and cellular level in the treated animals. But there is little data on the changes induced on molecular, genetic, proteomic level in the cell, upon treatment with SA extracts.

There is an emergence of different class of drugs, known as Epigenetic drugs. These therapeutic drugs, target proteins responsible for Chromatin remodelling, DNA methylation and histone modifications in every cell types (Kirk et al., 2008). These drugs are able to affect the neuronal-epigenetic landscape i.e. neuroepigenome and plasticity of the cell; along with showing anti-cancerous properties (Patnaik & Anupriya, 2019; Tremolizzo et al., 2014). Also, this class of drugs can be developed as Complementary and alternative medicine (CAM) and Integrative Medicine (IM); and claim to show no side effects [IM is the combination of Conventional medicines and CAM]; which cure both psychological and physiological dysfunctions (Kanherkar et al., 2017). Based on the available evidences from other studies we can speculate that, *Semecarpus anacardium* extracts may show potential use as an effective epigenetic drug in near future and once individual bioactive components are identified, molecular mechanisms of its action are understood it can be used to cure various ailments apart from cancer, inflammation and neurodegenerative diseases (Figure 1).

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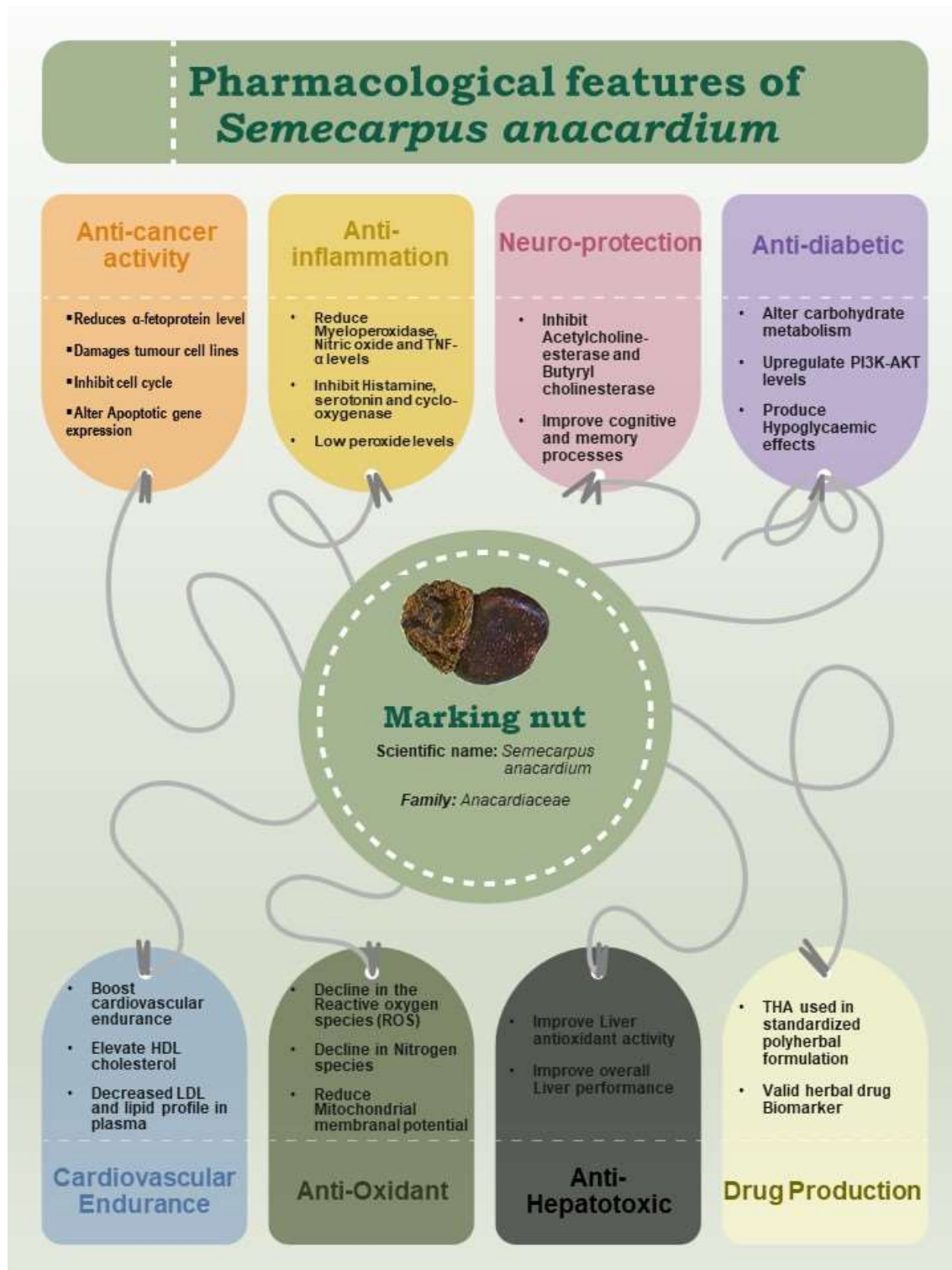


Figure 1: Overview of effects seen in *Semecarpus anacardium* extracts

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