Galangal, the multipotent super spices: A comprehensive review

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Abstract

Background: Galangal is highly appreciated for its potential applications in food and medicine. In spite of its usage in food and herbal medicine in countries like Indonesia and Thailand, very limited data is accessible about its potential applications in therapeutics and pharmacology. It has been reported to be utilized in herbal medicines for treatment against diseases like hemorrhoids, abnormal menstruation, abdominal discomfort, and inflammation, among others.

Scope and Approach: The widespread use of galangal in food and traditional medicine has fascinated researchers all over the world looking for its enhanced medicinal capabilities, new bioactive compounds with nutraceutical potentials, and probable uses in medicine and pharmacology. A number of literature search methods like searching the related contents with the keywords such as *Alpinia* sp., galangal, antiviral, cardiovascular, neuroprotective, bioactive compounds, phytochemicals etc. in the web search engines' such as the Google search, Web of Science, Scopus, PubMed etc. were implemented.

Key Findings and Conclusions: Conversely, there is no recent structured and ample review that summarizes the available data on these issues. In the current review, these topics are addressed in detail along with the investigation of scientific evidence supporting the vast applications of galangal in food and its medicinal properties, such as antiviral, cardiovascular and neuroprotective properties, together with the preclinical and clinical studies with galangal bioactive compounds.

Keywords: *Alpinia sp.;* galangal; antiviral; cardiovascular; neuroprotective; bioactive compounds

1. Introduction

Alpinia galanga (L.) Willd. (Zingiberaceae), usually called galangal or greater galangal, is a perennial plant native of Indonesia but cultivated in many parts of Asia being Thailand and Indonesia the main producers and suppliers. This plant has multiple applications from food to medicine (Figure 1). Galangal rhizomes are collected all over the year and employed in Asian gastronomy due to its spicy taste (Chudiwal, Jain, & Somani, 2010). *A. officinarum* Hance and *A. calcarata* Rosc. known as lesser galangal are two closely related species that have similar properties and uses of *A. galanga*, although this is the most important in terms of culinary uses. There is some confusion between the common terminologies galangal and galanga. Galangal designation is used to denominate *A. galanga* and its two closed related species *A. officinarum* Hance and *A. calcarata* Rosc., and galanga includes *Kaempferia galanga* L., an entirely different species (Ravindran, 2017).

Beyond its food uses, galangal has also been utilized for centuries in traditional medicine in several countries. In Ayurveda, Unani, Chinese and Thai folk medicine it is applied in the treatment of diarrhea and stomach-ache due to its carminative, stomachic, antispasmodic and antimicrobial properties (Mayachiew & Devahastin, 2008; X. Yang & Eilerman, 1999). There are also reports about its traditional use to treat hemorrhoids, abnormal menstruation and abdominal discomfort (Abubakar, Malami, Yahaya, & Sule, 2018). In India, the galangal rhizome, usually called *raasna*, is applied in several Ayurvedic formulations to threat rheumatism and inflammatory disorders and is also employed for the treatment of other ailments such as diabetes, dementia and neurodegenerative diseases (L. Arambewela & Wijesinghe, 2006; L. S. Arambewela, Arawwawala, Owen, & Jarvis, 2007; Indrayan, et al., 2009; Mundugaru, Sivanesan, Udaykumar, Prabhu, & Ravishankar, 2018; Ravindran, Pillai, Balachandran, & Divakaran, 2012). Galangal is one of the rejuvenator herbs included in preparations used to treat some chronic diseases (Srivastava & Shanker,

2012). Furthermore, this plant has also cosmetic and perfumery applications (Yang and Eilerman 1999). Several classes of compounds have been found in galangal, including flavonoids, terpenoids, saponins, phenolic acids and essential oils (Aziman, Abdullah, Noor, Kamarudin, & Zulkifli, 2014; Chudiwal, et al., 2010). The major bioactive compounds found are galangin, kaempferol, galangal acetate, and 1,8-cineole (Ghosh & Rangan, 2013; Hamad, Alifah, Permadi, & Hartanti, 2016; Jaju, et al., 2009; Ravindran, et al., 2012; Upadhye, Rajopadhye, & Dias, 2018). Although the galangal rhizome is the most used and investigated portion of the plant, the flowers can provide additional benefits since it was recently found that they have antioxidant and antimicrobial properties, and their chemical composition is distinct from that of rhizome (Tang, Xu, Yagiz, Simonne, & Marshall, 2018). According to this study, 1′-acetoxyeugenol acetate was the greatest compound found in flowers, and pentadecane and α-humulene the major presence in their essential oil.

The extensive use of galangal particularly in food and traditional medicine has attracted the attention of researchers seeking its medicinal properties, active compounds, mechanism of action and potential applications. However, there is no recent systematized and comprehensive review summarizing available data on these issues. In this review, we, therefore, address these topics in detail and evaluate scientific evidence supporting the food and therapeutic uses of these multipotent super spices.

2. Galangal in food

Galangal in food is mostly used in Indonesia, Thailand, Cambodia, China, and Malaysia but it is also utilized in north-east regions of India and Western Europe. The rhizome is the principal portion of the plant with culinary applications providing a sweet spicy taste to many dishes particularly in shellfish preparations (Ravindran, 2017). Galangal rhizome is particularly used in the elaboration of Thai curry paste and soup (Juntachote, Berghofer,

Siebenhandl, & Bauer, 2007). In Indonesia, this rhizome is used in soups, sauces, sambals, several kinds of meat and fishes, and in the preparation of vegetable curries. Combined with other condiments as garlic, ginger, chili and lemon, galangal is used to prepare a curry with shellfish frequently employed as an accompaniment to rice dishes. Although it is mostly used as a flavouring agent it can also be utilized to mask the undesirable odours of some kinds of meat, particularly red meat and seafoods, making their taste more delicate.

The smaller rhizomes are usually preferred instead of larger and hard roots that are more difficult to slice. Before used, the rhizomes must be washed and the outer skin removed, and then can be cut in small pieces, crushed, grated or shredded for the different culinary uses (Ravindran, 2017). When it is not possible to obtain the fresh rhizome it can be substituted by the dried one that gives an aromatic flavor similar to cinnamon.

Galangin, the spicy constituent of galangal and its derivatives, provides an exclusive and mild spicy sensation deprived of lingering effect, not so strong as capsaicin. This compound has multiple applications, e.g., in beverages, sweets, personal care products, as alcohol-enhancer or as an alcohol substitute in alcohol-free beverages (X. Yang & Eilerman, 1999).

Beyond the rhizomes, the flowers, flower buds and fruits of *A. galanga* are also edible. The aromatic and ephemeral galangal flowers are consumed raw or steamed in salads and soups, in pickles or mixed with chili past (L. Arambewela & Wijesinghe, 2006; Rachkeeree, et al., 2018; Ravindran, 2017).

The essential oil is used in beverages as liqueurs, namely Chartreuse and Angostura, and in soft drinks (Duke, 2002). A recent investigation showed that galangal flowers have high contents in dietary fibre and macro-elements as potassium and calcium (Rachkeeree, et al., 2018).

Nowadays, consumers search for food with functional characteristics beyond its nutritional properties. The actual tendency is to incorporate plant compounds or extracts in food products

improving their functional properties and shelf life. Plant compounds can be excellent alternatives to synthetic additives, which have been questioned due to their toxicity (Caleja, et al., 2018). In addition to the traditional uses in food, some investigations have been conducted in recent years concerning the potential of galangal to incorporate in food products like biscuits, meat, and sausages, to increase their preservation and/or functional properties (Juntachote, et al., 2007; Klunklin & Savage, 2018; Półtorak, et al., 2018; Poltorak, et al., 2019). Table 1 summarizes the main reports investigating the incorporation of galangal in food products. Overall, galangal delayed lipid oxidation of food products during storage due to its antioxidant and antimicrobial properties. The use of galangal extract in edible chitosan films to increase their antimicrobial properties has been also described in the literature (Mayachiew et al. 2010). Reviewed data indicates that galangal has the potential to be used in food industry applications in an actual context where the use of natural non-toxic food additives is a more convenient solution for consumers that desire food products without synthetic additives.

3. Phytochemistry and constituents of Galangal

Alpinia galanga and *Alpinia officinarum* are two of the most common galangal species which are members of the Zingiberaceae family and are of current interest in many scientific studies due to their ethnobotanical use, medicinal and non-medicinal, in some parts of the world (Abubakar, et al., 2018). These pharmacological attributes have been related to the phytochemical constituents in the different galangal species.

Phytochemicals are a heterogeneous group of compounds with a wide array of structural diversity and distribution. According to their metabolic biosynthetic pathway, phytochemicals can be classified into alkaloids, terpenes, and phenolic compounds (Croteau, Kutchan, & Lewis, 2015; Yahia, 2017). The phytochemicals found in galangal species belong mostly to

151 the group of the terpenes and phenolic compounds; also, the distribution of these compounds
152 may depend on the geographical dispersion of the galangal species (Croteau, et al., 2015;
153 Zhou, et al., 2018).
154
155 3.1. Phenolic Compounds
156 Phenolic compounds are metabolites derived from the secondary metabolism of plants. They
157 are phenylpropanoids biosynthesized from the shikimate pathway (Vogt, 2010). There is a
158 wide array of phenolic compounds varying in molecular weight, complexity, and distribution,
159 however, all phenolic compounds have an aromatic arene (phenyl) ring with at least one – OH
160 group attached (Croteau, et al., 2015). Furthermore, phenolic compounds are considered as
161 weak acids due to the lability of the phenolic hydroxyl group from the aromatic ring. These
162 compounds can be classified depending on their chemical diversity, and according to the
163 number of carbons in the molecule (Vermerris & Nicholson, 2006). Also, based on the
164 number and arrangement of carbon atoms, phenolic compounds can be classified into
165 phenolic acids, flavonoids, lignans, and stilbenes. Phenolic acids are further sub-classified in
166 hydroxycinnamic acid and hydroxybenzoic acid derivatives; whilst flavonoids can be mainly
167 sub-classified in anthocyanins, proanthocyanidins, condensed tannins, isoflavonoids,
168 flavones, flavonols, flavan-3-ols, and flavanones (R. G. Baradwaj, Rao, & Senthil Kumar,
169 2017; Croteau, et al., 2015; Gutiérrez-Grijalva, et al., 2018; Vermerris & Nicholson, 2006).
170 Some of the most commonly found phenolic compounds are represented in Figure 2.
171 Some of the phenolic compounds and their derivatives that have been previously identified in
172 several galangal samples are p-hydroxybenzoic acid, vanillic acid, ferulic acid, kaempferol-3-
173 O-methylether, kaempferol, apigenin, luteolin, and chrysin, 1'-acetoxyeugenol acetate, among
174 others (G. Huang, et al., 2018; Köse, et al., 2015).
175 3.1. Terpenes

Terpenes (also called terpenoids) comprise a group of around 30,000 secondary metabolites derived from a molecule of five-carbon isopentane units, often called isoprene units. These molecules are biosynthesized from the mevalonate pathway by terpene synthase enzymes and other enzymes such as cytochrome P450s. Terpenes can be classified depending on their number of carbons, for instance, monoterpenes are 10-carbon terpenoids, five-carbon terpenes are called hemiterpenoids, 15-carbon terpenoids are recognized as sesquiterpenes, diterpenes contain 20-carbon terpenoids, and triterpenes are 30-carbon terpenoids (Bathe & Tissier, 2019; Chen, Tholl, Bohlmann, & Pichersky, 2011; Croteau, et al., 2015). Terpenes have been associated with some pharmacological properties of herbs and spices. They have been studied for their antimicrobial, anticancer, anti-inflammatory, and anti-diabetic properties (Leyva-López, Gutiérrez-Grijalva, Vazquez-Olivo, & Heredia, 2017; Tang, et al., 2018).

As seen in Figure 3, some of the reported terpene compounds identified in *A. galanga* and *A. officinarum* are galangalditerpene A, galangalditerpene B, α-terpineol, 1,8-cineole, and α-pinene among others (Khumpirapang, Pikulkaew, Anuchapreeda, & Okonogi, 2018; Manse, et al., 2017; Manse, et al., 2016; Zeng, Lu, Zhang, & Jiang, 2015).

4. Extraction of bioactive compounds from Galangal

Phytochemicals such as phenolic compounds and terpenes are of growing interest due to their potential health benefits in humans. The extraction of bioactive compounds from galangal has been reported by conventional and non-conventional methods, among the most widely reported are the conventional methods using chemical solvents. As is commonly known, the extraction of the non-polar compounds is usually performed with organic non-polar solvents such as acetone, hexane, chloroform, or a mix of them. While, the polar compounds are usually extracted with polar solvents such as water, ethanol, methanol, alone or in

combination (Hasbay & Galanakis, 2018; Saldaña, Gamarra, & Siloto, 2009). The general scheme of extraction of bioactive compounds from galangal is shown in Figure 4.

Nonetheless, to date, almost all reports regarding the extraction of bioactive compounds from galangal use organic solvents. For instance, ethanol and aqueous ethanol were used by Huang et al. (G. C. Huang, et al., 2018), who identified polar compounds such as phenolic and derivatives like p-hydroxybenzoic acid, vanillic acid, ferulic acid, kaempferol-3-O-methylether, and kaempferol-3,4-O-dimethylether, among others. Similarly, 50% ethanol was used to obtain phenolic compounds such as kaempferol, p-benzoic acid, p-coumaric acid, apigenin, luteolin, and quercetin (Köse, et al., 2015). On the other hand, some ethanolic extracts have been performed as reported by other works, but non-polar compounds were the aim of their study. In this category we find the work by Bian et al. (Bian, et al., 2014), who obtain ethanol extracts from *A. galanga* and identified terpenes like galangol A, galangol B, and galangol C. Furthermore, non-polar compounds from galangal have been identified from ethanol extracts later resuspended in methanol and hexane, where the GC analysis showed the presence of α-humulane, β-guaiene, pentadecane, humulene oxide, bulnesol, α-bisabolol, β-farnesol; whilst LC-MS/MS analysis showed the presence of 1'-acetoxyeugenol acetate (Tang, et al., 2018).

The extraction of essential oils from the seeds of *A. galanga* reported by Zeng et al. (Zeng, et al., 2015), was performed by maceration with 95% ethanol thrice. Once the extracts were obtained, they were evaporated under vacuum to dryness and re-suspended in water. After that, the solution was partitioned with petroleum ether and ethyl acetate. This had a significant effect on the essential oil distribution and bioactive properties, as the ethyl acetate fraction showed protective effects of the PC-12 cells against H_2O_2 damage. Furthermore, the authors reported higher cytotoxic activity of petroleum ether and ethyl acetate extracts on HeLa, A549, HepG2, and SMMC-7721 cells, whilst water extracts did not have inhibition effect on

cancer cells. The higher bioactive properties of the petroleum ether and ethyl acetate fractions was related to their essential oil recovery due to the polarity of the constituents like 1'S-1'-acetoxyeugenol acetate, 1'S-1'-acetoxychavicol acetate, 2-propenal,3-[4-(acetyl-oxy)-3-methoxyphenyl], isocoronarin D, and caryolane-1,9β-diol (Zeng, et al., 2015).

As far as our literature search can ascertain, the study by Xin et al. (M. Xin, et al., 2017), is one of the few reports aimed to obtain bioactive compounds from *A. officinarum* rhizomes by supercritical fluid CO_2 extraction (SFE). The SFE is an environmental friendly technology, which reduces solvent disposal, minimizes thermal degradation, and retains the target components without any modification. Thus, the authors aimed to isolate essential oils from *A. officinarum* by SFE. The essential oils of *A. officinarum* were extracted by a SFE at 50 ºC, 5-6 Mpa, and 30 L/h of CO_2 flow for 2.5 h (M. Xin, et al., 2017). The SFE showed a higher yield of essential oil from *A. officinarum* than hydro-distillation (HD) (a conventional technique to isolate essential oils), resulting in 11.1% and 0.62%, respectively. This was attributed to the faster diffusivity of supercritical fluids than liquids (Sunarso & Ismadji, 2009). Furthermore, the authors reported a differential response in the essential oil content from both SFE and HD samples, which was related to the different polarities in the SFE method used and the HD method.

Another study by Yuan et al. (Yuan, Lin, Huang, & Li, 2017), tested different extraction methods to obtain essential oils from *A. officinarum*. They extracted essential oils by steam distillation (SD), ultrasonic-assisted solvent extraction (UAE), and supercritical fluid extraction (SFE). The essential oil composition showed significant differences between methods, thus authors suggested that the method of choice will depend on the aimed product (Yuan, et al., 2017). For instance, the most abundant essential oil in samples from the three extraction methods was 1,8-cineole (also known as eucalyptol). An important factor suggested as a determinant for the differences observed in essential oil composition, was the

extraction temperature of each method, whilst the UAE and SFE methods do not reach above 45 ºC, the steam distillation method does, thus some labile components might be degraded. Also, Luo et al. (J. C. Luo, et al., 2010), reported the SFE of diarylheptanoid compounds from *A. officinarum*. UPLC-ESI-MS analysis of the SFE extracts showed that they contained around 23 diarylheptanoids, which are compounds with a 1,7-diarylheptane skeleton with anti-inflammatory and antioxidant properties. Details of the SFE extraction of diarylheptanoids is not given by the authors (Lv & She, 2010).

The extraction methods of galangal phytochemicals are summarized in Table 2.

5. Medicinal effects of active constituents from Galangal

5.1 Anticancer, antiviral and anti-inflammatory properties of galangal:

In Figure 5, the structure of compounds extracted from *A. officinarum* can be observed. The first compound (7-(4-hydroxyphenyl)-1-phenyl-3-heptanonewhich) has a moderate level of anticancer activity (compared to 5-fluorouracil as control) with IC_{50} values less than 50µg/mL against HepG2 and MCF-7 cancer cell line (Figure 5) (Liu, Liu, Guan, & Liang, 2014).

The second compound (1,7-diphenyl-4-en-3-heptanone) has a very satisfactory platelet-activating factor (PAF) receptor binding antagonist activity with an IC_{50} value of 5µM that has the potential to inhibit PAF mediated inflammatory diseases (Fan, Kang, Han, & Han, 2007). The third compound (1,7-diphenyl-3,5-heptanedione) was reported to have good antibacterial activity against *Helicobactor pylori* with MIC values of 9-30 µg/mL suggesting its future use as an antibacterial molecule (B.-B. Zhang, Dai, Liao, & Ding, 2010). Honmore et al. (Honmore, et al., 2016), demonstrated that the fourth compound (1,7-diphenyl-5-ol-3-heptanone) has the potential to inhibit the activity of COX-2 by binding to its active site thereby acting as an efficient anti-inflammatory molecule (Figure 5). The fifth

compound (1,7-iphenyl-5-hydroxy-3-heptanone (dihydroyashabushiketol)) has been reported by Kim et al. 2003 as exhibiting 5α-reductase inhibitory activity. This is a key enzyme responsible for reductive conversion of testosterone to 5α-dihydrotestosterone (a more active androgen) and its efficient inhibition can be a therapeutic target for treatment of androgen-dependent diseases, such as benign prostate hyperplasia, male pattern baldness and acne (Figure 5) (Kim, et al., 2003). Reddy et al. (Purushotham Reddy, et al., 2012), demonstrated that the seventh compound which is alpinoid-C exhibited very promising anticancer activity against both human leukemia and mouse melanoma (B16-F10) cancer cell lines. Similarly, the ninth compound (3,5-dihydroxy-1,7-diphenylheptane) has been reported by Matsuda et al. (Matsuda, Ando, Kato, Morikawa, & Yoshikawa, 2006), as having a very good inhibitory effect on the generation of nitric oxide in lipopolysaccharide-activated macrophages thereby downregulating the pathway leading to inflammation and multistage carcinogenesis at inflammatory sites (Matsuda, et al., 2006).

In Figure 6, the structure of important bioactive compounds extracted from *Alpinia. galanga* can be perceived. The first compound named, 1 '-acetoxychavicol acetate was demonstrated to have superior anticancer activity against sarcoma 180 ascites in mice (Itokawa, Morita, Sumitomo, Totsuka, & Takeya, 1987). This compound also inhibits human immunodeficiency virus type 1 replication by blocking Rev transport (Ye & Li, 2006). The second compound called, 1’-acetoxyeugenol acetate was demonstrated to have very potential antitumor activity and may be useful as a future natural product based anticancer molecule (Morita & Itokawa, 1988; Zeng, et al., 2015). The third compound, (trans-3,4-dimethoxycinnamyl alcohol) being one of the major phyto-compound in *Alpinia galanga* extract was demonstrated to have anti-proliferative effect by inducing apoptosis in human breast carcinoma cell line (Samarghandian, Afshari, & Hosseini, 2014). The fourth (1,7-bis(4-hydroxyphenyl)-1,4,6-heptatrien-3-one) and fifth (bisdemethoxycurcumin) compound was

demonstrated by Lo et al. (Lo, et al., 2013), and reported to possess an effective anti-proliferative bioactivity against the human melanoma cell line and significantly inhibited the proliferation of melanoma cells (Lo, et al., 2013).

The extract of *A. officinarum* has been used for treatment against poliovirus, respiratory syncytial virus, herpes simplex virus type 1 and measles virus *in vitro*. Respiratory syncytial virus (rsv) infection is a serious form of illness in both the elderly and children under 2 years and causes serious pneumonia and bronchitis (Basri, Taha, & Ahmad, 2017; Devi, Bagyalakshmi, & Gayathri, 2019). Konno et al. (Konno, et al., 2011), demonstrated that seven of the nine diarylheptanoids isolated from *A. officinarum* exhibited very satisfactory antiviral activity against rsv, poiovirus, and measles virus with good EC_{50} values. In another study, Sawamura et al. (Sawamura, et al., 2009) demonstrated that diarylheptanoids, which is the bioactive ingredient of this species exhibited important antiviral activity against influenza virus under *in vitro* conditions (Figure 7). Tewtrakul et al. demonstrated that *A. galangal* methanolic extract exhibited a promising antiviral activity against the human immunodeficiency virus type-1 (HIV-1) and human cytomegalovirus (HCMV) (Tewtrakul, Subhadhirasakul, & Kummee, 2003).

5.2 Cardiovascular and neuroprotective effects of galangal:

Reactive oxygen species and reactive nitrogen species (ROS/RNS) that originates from mitochondria can be considered as the important mediators of inflammation that cause severe damage to cells and tissues that manifest the onset of cardiovascular and neurodegenerative diseases (Honmore, et al., 2016) (Figure 7). It was shown using computational tools that the bioactive compounds like galangin and 5-hydroxy-7-(4″-hydroxy-3″-methoxyphenyl)-1-phenyl-3-heptanone could be able to exhibit anti-inflammatory and antioxidant activity by inhibiting the COX-2 activity and release of

serotonin, kinin, and histamine (Honmore, et al., 2016). Lipid metabolism disorders like hypercholesterolaemla and hypertriglyceridemia are important mediators of atherosclerotic cardiovascular, cerebrovascular and ischemic heart diseases. In this connection, it was shown that extracts of *A. galangal* are very effective in decreasing the level of low-density lipoprotein in the blood serum thereby countering the hazards associated with hyperlipidemia (Achuthan & Padikkala, 1997). Nowadays obesity is an alarming health issue and is an important risk factor for the genesis of multiple recurring diseases such as hypertension and coronary heart diseases. To address this issue ethanolic extracts of *A. officinarum* may be considered as having high anti-obesity potential since can satisfactorily suppress body weight gain and also improve the healthy lipid profile (Bukvicki D, et al., 2018; Dao-Zong Xia, Xin-Fen Yu, Hui-Ming Wang, Qi-Ya Ren, & Chen, 2010). Ravichandra et al. (Ravichandra, Hanumantharayappa, & Papasani, 2014), reported that galangin (3,5,7-trihydroxy-2-phenylchromen-4-one), which is present in *Alpinia galangal* rhizome extract possess strong antioxidant activity and has the potential to maintain cell membrane integrity, reduce oxidative stress and rectify cardiac systolic/diastolic dysfunction in the cardiac myocytes stressed with doxorubicin (Ravichandra, et al., 2014). High fat intake in the form of saturated fat increases the cholesterol level in blood that paves the way for cardiovascular disease (Briggs, Petersen, & Kris-Etherton, 2017). Broiler chicken meat is enjoyed worldwide but is taken in limited quantity due to high fat content (Adriani, 2013). In this context Adriani, 2013, reported that broiler chicken fed with *Alpinia galanga* juice exhibited reduced level of triglyceride in broiler blood which may be healthier for regular consumption (Adriani, 2013). Dyslipidemia is very important factor for the onset of cardiovascular diseases and a study revealed that a combined treatment with *Phyllanthus embilica* and *Alpinia galanga* extracts could effectively lower the level of circulating low density lipoprotein cholesterol by

enhancing the level of expression of low density lipoprotein receptor gene (Tirawanchai, et al., 2019).

Neuropathology of Alzheimer's disease (AD) is featured by the gathering of extracellular amyloid plaques in the brain which is made up of amyloid beta-protein (Donald L. Price & Sisodia, 1994). The integrity of the neuronal membrane is regulated by Na^+/K^+ATPase which is essential for multiple neuronal functions and it has been reported that in Alzheimer's disease a considerable reduction in the activity of Na+/K+ ATPase especially in thalamus and nucleus takes place. In context to this Singh et al. (2011) demonstrated that mice treatment with *A. galanga* fractions induced acceleration of cognitive function and increase Na^+/K^+ ATPase, antioxidant response while decreasing acetylcholinesterase activity (Hanish Singh, et al., 2011; Poonam, Choudhary M, Kumar D, & V, 2019) (Figure 7). ROS mediated oxidative stress affects the biomolecules (lipids, proteins and DNA) thereby disrupting the cellular function and integrity. These cellular damages switch on the genesis of neurodegenerative disorders like Parkinson's disease and Alzheimer's disease. In connection to this (2r, 3s)-pinobanksin-3-cinnamate that is a new flavonone extracted from the seeds of *Alpinia galanga* exhibited satisfactory in vitro neuroprotective effects by acting as a potential antioxidant molecule thereby downregulating oxidative stress (B. R. Xin, Liu, Kang, & Chan, 2014).

6. Preclinical and clinical studies on active compounds from Galangal:

In one study to prevent *in vivo* two-stage carcinogenesis using mice model, it was demonstrated that bioactive diarylheptanoids present in methanol extract of galangal exhibited remarkable antitumor-promoting activity suggesting the future prospect to design anticancer drug using bioactive components of galangal (Yasukawa, et al., 2008). Hot water-soluble polysaccharide extracts of *A. galangal* exhibited immune-stimulating activity as it very

appreciably enhanced the proliferation of the murine spleen cells thereby enhancing the immune response efficacy of phagocytic and lymphocytic systems (Bendjeddou, Lalaoui, & Satta, 2003). Galagin which is the active component of *A. officinarum* also has antiobesity effect as demonstrated by experiments performed on mice model fed with a high-fat diet. The findings suggest that ethanol extract of *A. officinarum* could satisfactorily reduce the expression of c/ebpα, fatty acid synthase, srebp-1, and ppar-γ in the liver and adipose tissue suggesting the future use of its ethanol extract for preparing a natural based product to be used as an antiobesity therapeutic agent. Cisplatin which is a chemotherapeutic anticancer agent has important side effects like neurotoxicity and nephrotoxicity. Huang et al. (Huang, et al., 2017), showed that galangin extracted from *A. officinarum* could appreciably ameliorate the nephrotoxicity due to cisplatin in mice by ameliorating oxidative stress and inflammation through inactivation of NF-ƙB and ERK pathways (Huang, et al., 2017).

Jakobsen and Giversen (Jakobsen & Giversen, 2015), filed a patent on the preparation of orally ingestible dosages of tablets/capsules containing granulate extracts from *A. galanga* or *A. conchigera* containing high levels of 1'S-1'-acetoxychavicol acetate (ACA) for the cure of male infertility which is caused by low sperm count and/or by low sperm motility. In another Chinese patent, it was reported that extracts of *A. officinarum* can be used for the preparation of tablets, capsules, pills, powders, granules, oral liquid formulations for clinical use, or can be injected to treat dysmenorrhea due to its anti-inflammatory effects (Li Youbin, et al., 2015).

7. Challenges and future prospect associated with galangal.

Medicinal plants like galangal are very important natural resources considering their disease healing properties and needs mass cultivation for their easy availability to industries and people who rely on herbal medicine. But due to rapid decrease in cultivable land,

deterioting soil quality and unstable weather conditions, mass cultivation and conservation by conventional method has become an obstacle in the present scenario. To address this issue, *in vitro* conservation of micro-propagated plants is a safe and reliable method to protect and quickly propagate galangal (Parida, Mohanty, & Nayak, 2011). Many of the researchers engaged with bioactive phyto-compound extraction, separation and identification from galangal sp, mostly rely on the Soxhlet apparatus for initial extraction from crude plant material. However this method of extraction is time consuming and needs large amount of solvent. Moreover high temperature for extended period of time significantly impact the quality of the yield as most galangal plant extract ingredients are heat labile molecules which may undergo minor structural changes thereby reducing their therapeutic efficiency. Microwave assisted extraction seems to be a suitable alternative to this method due to shorter extraction and high temperature exposure time length (30 minute or less) that preserves the integrity of the bioavtive molecules. Less solvent, minimal environmental pollution and high efficiency are extra advantages associated with microwave assisted extraction (Muhamad, et al., 2017).

The active components in galangal extracts are suitably soluble in solvents with low polarity but less soluble in water thereby reducing its bioavailability due to poor intestinal absorptivity. To resolve this issue more researches are needed to be carried out to prepare various nano-formulations containing the active components from galangal sp. that could have improved aqueous solubility, enhanced dispersibility, higher cell membrane penetrability and hence could enhance the therapeutic efficiency of the compounds. Also metal oxide nanoparticles are highly bioactive and finds wide applications from medicine to agriculture (Upadhyaya, et al., 2018). Nano conjugates of metal oxide nanoparticles and galangal derived bioactive molecules may be synthesized which may have the potential to

exhibit synergistic as well as multi-target therapeutic efficiency resulting in faster disease healing in near future.

Further studies, particularly *in vivo* studies, are required to accurately evaluate the biological properties of galangal and to confirm its pharmacological relevance. Investigation towards the use of galangal in the development of novel functional healthy products is also needed. Additionally, aspects related to the standardization of the constituents of galangal extracts deserve more attention in the future. Considering the wide range of phytochemicals and their bioactivity, the plant may be explored in finding future drug leads which can be helpful in curing various diseases.

Conclusions

Galangal contains numerous bioactive compounds with varied pharmacological and medicinal properties. Despite the usage of galangal in food and herbal medicine in countries like Indonesia and Thailand, very limited data is available about its therapeutics and pharmacology. Significantly very limited reviews were found on the medicinal potential of this species with special reference to its antiviral, cardiovascular and neuroprotective effects, together with its preclinical and clinical studies. This review discusses the above-said issues in detail and scientific manner which could be beneficial for the scientific community for the development of drug formulations for the benefit of society.

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761

762 **Table 1. Summary of the main publications reporting the inclusion of galangal in food**

763 **products.**

Food product	Main achievement(s)	Reference
Biscuits	Galangal powder in combination with other spices and defatted green-lipped mussel powder improve the protein and fiber contents, and antioxidant properties of the biscuits	(Klunklin & Savage, 2018)
Cooked ground pork	Dried galangal powder (0.350%) has a higher capacity to inhibit lipid oxidation in cooked pork than its ethanolic extract (0.1%)	(Juntachote, Berghofer, Siebenhandl, & Bauer, 2006)
Cooked ground pork	Dried galangal powder (0.05, 0.10 and 0.15%) and its ethanolic extract (0.17, 0.43 and 0.51%) protected cooked ground pork against lipid oxidation during storage in a dose-dependent way, although dried powder was more effective	(Juntachote, et al., 2007)
Raw minced beef	Galangal extract (0.05 and 0.10%, w/w) extended the shelf-life of crushed beef	(Cheah & Gan, 2000)
Raw and cooked minced beef	Galangal extract (10%, w/w) inhibited/minimised/delayed lipid oxidation in minced beef	(Cheah & Abu Hasim, 2000)
Sausages	Ground galangal (0.22 g/kg) delayed lipid oxidation and microbial growth, and improve antioxidant and anti-inflammatory properties of sausages during storage	(Półtorak, et al., 2018)
Sausages	Ground galangal (0.022%) improve antioxidant and anti-inflammatory properties of sausages with good sensorial acceptability	(Poltorak, et al., 2019)

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765

766 **Table 2. Summarization of the phytochemicals identified in galangal (*A. galanga* and *A.***

767 ***officinarum*).**

Galangal	Solvent	Analysis method	Constituents	Reference
A. galanga seeds	95% Ethanol, then re-extracted with petroleum ether, ethyl acetate and water fractions	Semipreparative HPLC, and ^{1}H-NMR, ^{13}C-NMR, DEPT135 and HMPQC spectra	Ethyl acetate fraction: 1'S-1'-acetoxyeugenol acetate, 1'S-1'-acetoxychavicol acetate, 2-propenal,3-[4-(acetyl-oxy)-3-methoxyphenyl], isocoronarin D, caryolane-1,9β-diol	(Zeng, et al., 2015)
	95% Ethanol	Preparative HPLC and ^{1}H and ^{13}C-NMR	Galangol A, galangol B, galangol C	(Bian, et al., 2014)
A. galanga	Methanol	1H-NMR, 13C-NMR	1-dehydro-3-hydro-[2]-gingerdione, zerumbone, zerumbone epoxide, α-humulene, β-sitostenone, stigmasta-4,22-dien-3-one, p-hydroxybenzoic acid, vanillin, vanillic acid, syringaldehyde, ferulic acid, kaempferol-3-O-methylether, kaempferol-3,4-O-dimethylether, kaempferol-3-O-rhamnoside, kaempferol-3-O-(2''-O-acetyl)rhamnoside, kaempferol-3-O-(3''-O-acetyl)rhamnoside, kaempferol-3-O-(4''-O-acetyl)rhamnoside, kaempferol-3-O-(2'',4''-O-diacetyl)rhamnoside, kaempferol-3-O-(3''',4''-O-diacetyl)-rhamnoside	(G. Huang, et al., 2018)
	95% Ethanol	2D NMR	Galanganone A, galanganone B, galanganone C	(W. Yang, Gao, Li, Miao, & Wang, 2015)

	Ethanol and 50% ethanol	UHPLC-PDA	(E)-p-coumaryl alcohol ethyl ether, (E)-p-acetoxycinnamyl alcohol	(Chansriniyom, et al., 2018)
	Accelerated solvent extractor with petroleum ether and ethyl acetate	HPLC-DAD	Chrysin (5,7-dihydroxy flavone)	(Lakshmi, et al., 2019)
	Ethanol extracts were later resuspended in methanol and hexane	GC-FID	Dimethyl pyrazine, dimethyl trisulfide, mercaptomethylbutanol, β-elemene, α-humulane, β-guaiene, pentadecane, humulene oxide, bulnesol, α-bisabolol, β-farnesol	(Tang, et al., 2018)
		LC-MS/MS	1'-Acetoxyeugenol acetate	
	80% aqueous acetone	NMR	Galangalditerpene A, galangalditerpene B, galangalditerpene C, clovane-2β,9α-diol, caryolane-1,9β-diol, (-)-2-oxoisodauc-5-en-12-al, kobusone, galanolactone, €-15,16-bisnorlabda-8(17),11-diene-13-one	(Manse, et al., 2017)
	Hexane	HPLC	1'S-1'-Acetoxychavicol	(R. Baradwaj, Rao, & Kumar, 2017)
	80% Aqueous acetone	^{1}H-NMR, ^{13}C-NMR, ESIMS, and HRESIMS mass spectrometers	Galangol D diacetate, 1'S-1'-acetoxy-chavicol acetate, 1'S-1'acetoxteugenol acetate, 1'S-1'-hydroxychavicol acetate, 1'S-1'-hydroxyeugenol acetate, 1'S-1'acetoxydihydrochavicol acetate, 1-(4-hydroxyphenyl)-1-propanone, trans-p-coumaryl acetate, trans-p-	(Manse, et al., 2016)

			acetoxycinnamoyl alcohol, trans-p-coumaryl alcohol, trans-p-coumaryl aldehyde, trans-p-coumaryl alcohol γ-O-methyl ether, trans-coniferyl alcohol 4-O-acetate, trans-coniferyl alcohol, trans-coniferyl aldehyde, 4-hydroxybenzaldehyde, 4-hydroxy-3-methoxy-benzaldehyde	
	Hydrodistillation	GC-MS	α-Pinene, camphene, β-pinene, limonene, 1,8-cineole, γ-terpinene, terpinolene, fenchone, linalool, fenchol, nonanal, camphor, borneol, terpinen-4-ol, myrtenal, α-terpineol, myrtenol, cis-carveol, α-fenchyl acetate, carvone, geraniol, bornyl acetate, methyl cinnamate, α-terpinyl acetate, α-cubebene, α-copaene, β-elemene, α-gurjunene, α-cedrene, α-bergamotene, (z)-β-farnesene, (E)-β-farnesene, α-farnesene, germacrene-D, zingiberene, α-selinene, α-muurolene, cubenol, γ-cadinene, δ-cadinene, E-nerolidol, germacrene-D-4-ol, guaiacol, γ-eudesmol, bulnesol, α-bisabolol, Z,Z-farnesol	(Nampoothiri, Menon, Esakkidurai, & Pitchumani, 2016)
	Hydrodistillation	GC-MS	α-Pinene, camphene, sabinene, β-pinene, β-myrcene, α-terpipene,	(Khumpirapang, et al., 2018)

			1,8-cineole 1,3,6-octatriene, γ-terpinene, α-terpinolene, borneol, α-terpineol, terpinen-4-ol, 2,butenal, chavicol, 4-allylphenyl acetate, eugenol, geranyl acetate, eugenol, geranyl acetate, methyl eugenol, β-selinene, β-farnesene, germacrene-D, β-bisaboloene, β-sesquiphellandrene	
	Hexane	HPLC	1'S-1'-Acetoxychavicol	(R. Baradwaj, et al., 2017)
A. officinarum	50% Ethanol	LC-MS/MS	Kaempferol, pyrogallol, p-OH benzoic acid, p-coumaric acid, apigenin, luteolin, quercetin, isorhamnetin	(Köse, et al., 2015)
	Consecutive extraction with hexane, chloroform, and methanol	UV, IR, MS, ^{1}H-NMR, and ^{13}C-NMR	Galangin, kaempferide, kaempferide -3-O-β-D-glucoside	(Eumkeb, Sakdarat, & Siriwong, 2010)
	Methanol	LC-MS/MS	Nootkatone, yakuchinone A, diarylheptanoid, hannokinol, hexahydrocurcumin, galangin, pinocembrin, isorhamnetin, luteolin, rutin, apigenin, quercetin, acacetin, chrysin, tectochrysin, izalpinin, kaempferol, kaempferide	(J.-Q. Zhang, et al., 2015)
	Supercritical Fluid Extraction	UPLC-ESI-MS/MS	5-hydroxy-1-(4-hydroxy-3-methoxylphenyl)-7-(3,4-dihydroxy-5-methoxylphenyl)-3-heptanone, 5-hydroxy-1-(3,4-dihydroxyphenyl)-7-(4-hydroxy-3-methoxyphenyl)-3-	(J. Luo, et al., 2010)

			heptanone, 5-hydroxy-1-(4-hydroxyphenyl)-7-(4-hydroxy-3-methoxylphenyl)-3-heptanone, 5-hydroxy-7-(4-hydroxyphenyl)-1-(4-hydroxy-3-methoxylphenyl)-3-heptanone, 5-hydroxy-1,7-bis(4-hydroxy-3-methoxylphenyl)-3-heptanone, 5-hydroxy-1-phenyl -7-(3,4-dihydroxy-5-methoxylphenyl)-3-heptanone, 5-hydroxy-1-phenyl-7-(3,4-dihydroxyphenyl)-3-heptanone, 3,5-dishydroxy -1-(4-hydroxyphenyl)-7-phenylheptane, 3,5-dishydroxy-1-(4-hydroxy-3-methoxylphenyl)-7-phenylheptane, 1-(4-hydroxyphenyl)-7-(4-hydroxy-3-methoxylphenyl)-4-en-3-heptanone, 5-hydroxy-1-phenyl -7-(4-hydroxyphenyl) -3-heptanone, 5-hydroxy-1-phenyl-7-(4-hydroxy-3-methoxylphenyl)-3-heptanone, 3,5-dihydroxy-1,7-bisphenylheptane, 1-phenyl-7-(4-hydroxyphenyl)-4-en-3-heptanone, 1-phenyl-7-(4-hydroxy-3-methoxylphenyl)-4-en-3-heptanone, 5-hydroxy-	

			1,7-bisphenyl-3-heptanone, 1-(4-hydroxyphenyl)-7-phenylhepta-3,5-dione, 1-(4-hydroxy-3-methoxylphenyl)-7-phenylhepta-3,5-dione, 5-hydroxy-1-(4-hydroxy-3-methoxylphenyl)-7-phenyl-4,6-dien-3-heptanone, 1,7-bisphenyl-4-en-3-heptanone, 1,7-bisphenylhepta-3,5-dione, 5-hydroxy-1,7-bisphenyl-4, 6-dien-3-heptanone, officinarumane C	

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769

Figure legends

Figure 1. Main uses of galangal.

Figure 2. Graphical representation of the structures of common phenolic compounds identified in some galangal species such as *Alpinia galanga* and *Alpinia officinarum*. Figures adapted from the PubChem database. a) apigenin, b) chrysin, c) galangin-3-methylether, d) galangin, e) kaempferide, f) kaempferol-3-methylether, g) kaempferol-3-rhamnoside, h) pinocembrin, i) zingerone

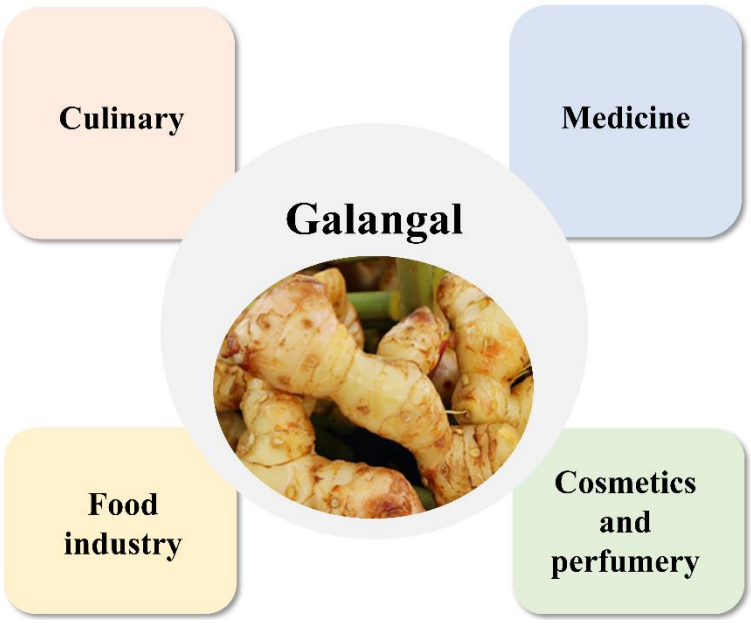
Figure 3. Graphical representation of the structures of common terpenes identified in some galangal species such as *Alpinia galanga* and *Alpinia officinarum*. Figures adapted from the PubChem database. a) α-pinene, b) α -terpineol, c) 1,8-cineole.

Figure 4. Scheme of the most common conventional and emerging methods to extract and analyze galangal bioactive compounds.

Figure 5. Structure of compounds extracted from *Alpinia officinarum*: (A) 7-(4-hydroxyphenyl)-1-phenyl-3-heptanone; (B) 1,7-diphenyl-4-en-3-heptanone; (C) 1,7-diphenyl-3,5-heptanedione; (D) 1,7-diphenyl-5-ol-3-heptanone; (E) 1,7-diphenyl-5-hydroxy-3-heptanone (dihydroyashabushiketol); (F) trans,trans-1,7-diphenyl-5-ol-4,6-dien-3-hepatnone; (G) (4E,6R)-6-dydroxy-1,7-diphenylhept-4-en-3-one (alpinoid C); (H) 7-(4-hydroxy-3-methoxyphenyl)-1-phenylheptane-3,5-diol; (I) 3,5-dihydroxy-1,7-diphenylheptane; (J) 3,6-furan-1,7-diphenylheptane.

Figure 6. Structure of compounds extracted from *Alpinia galanga*: (A) 1 '-acetoxychavicol acetate ; (B) 1’-acetoxyeugenol acetate; (C) trans-3,4-dimethoxycinnamyl alcohol; (D) 1,7-bis(4-hydroxyphenyl)-1,4,6-heptatrien-3-one; (E) bisdemethoxycurcumin

Figure 7. Therapeutic targets of galangal.



794

795 **Figure 1.**

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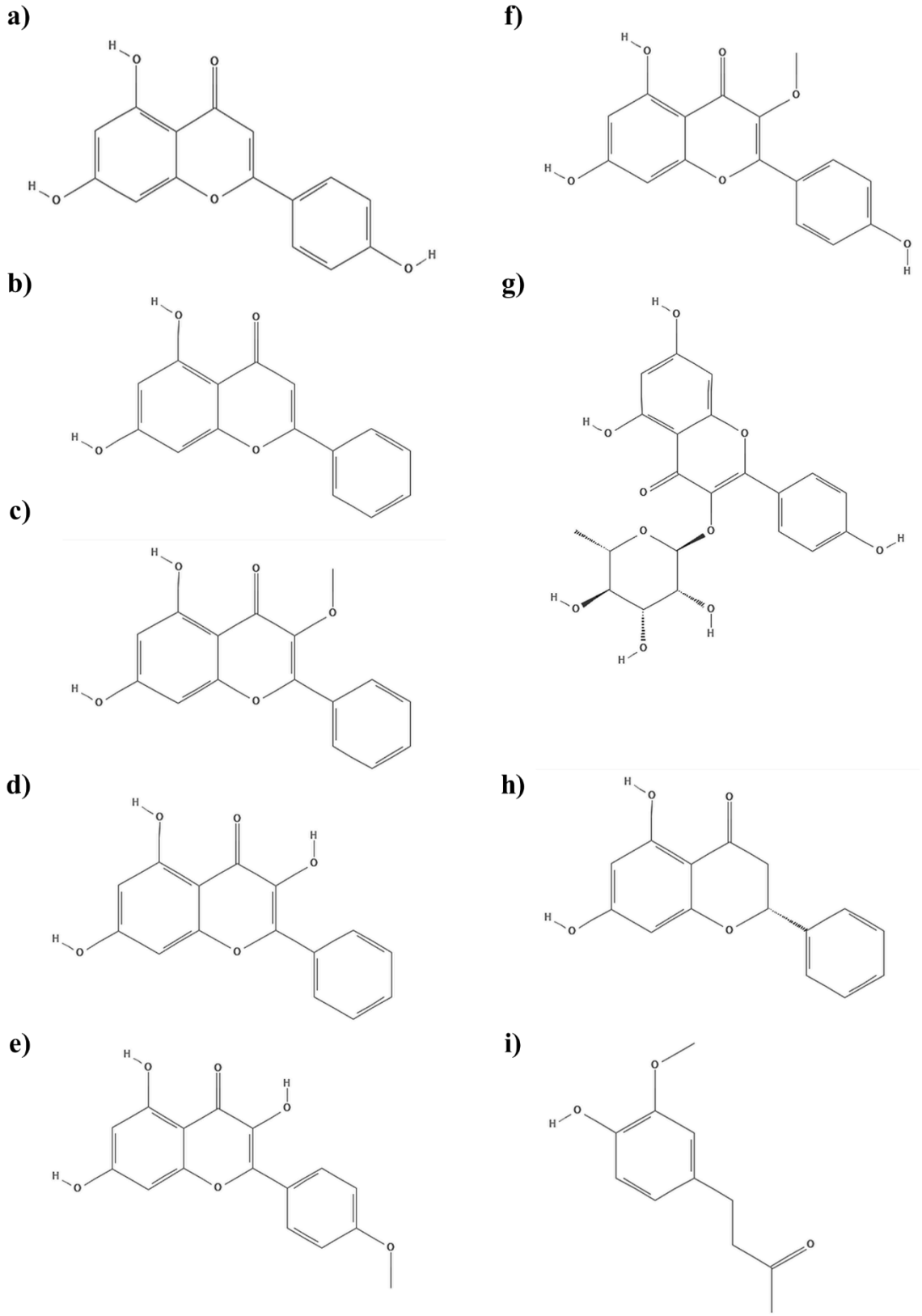

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798 **Figure 2.**

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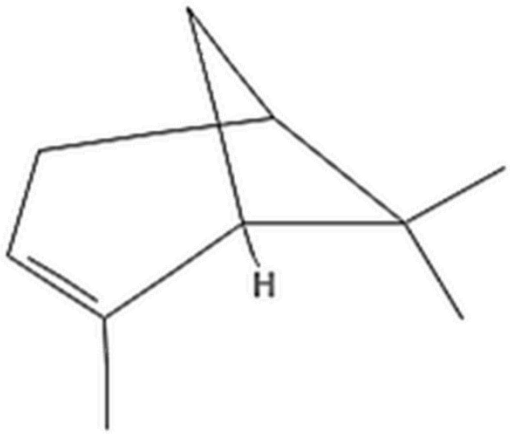

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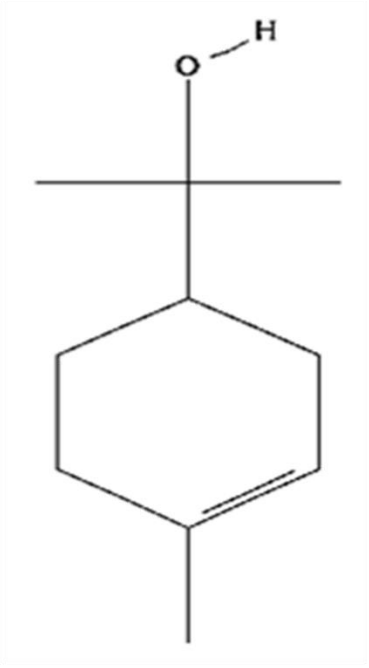

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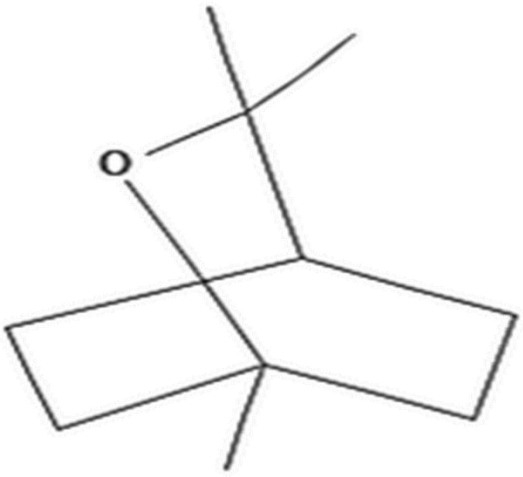

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800 **Figure 3.**

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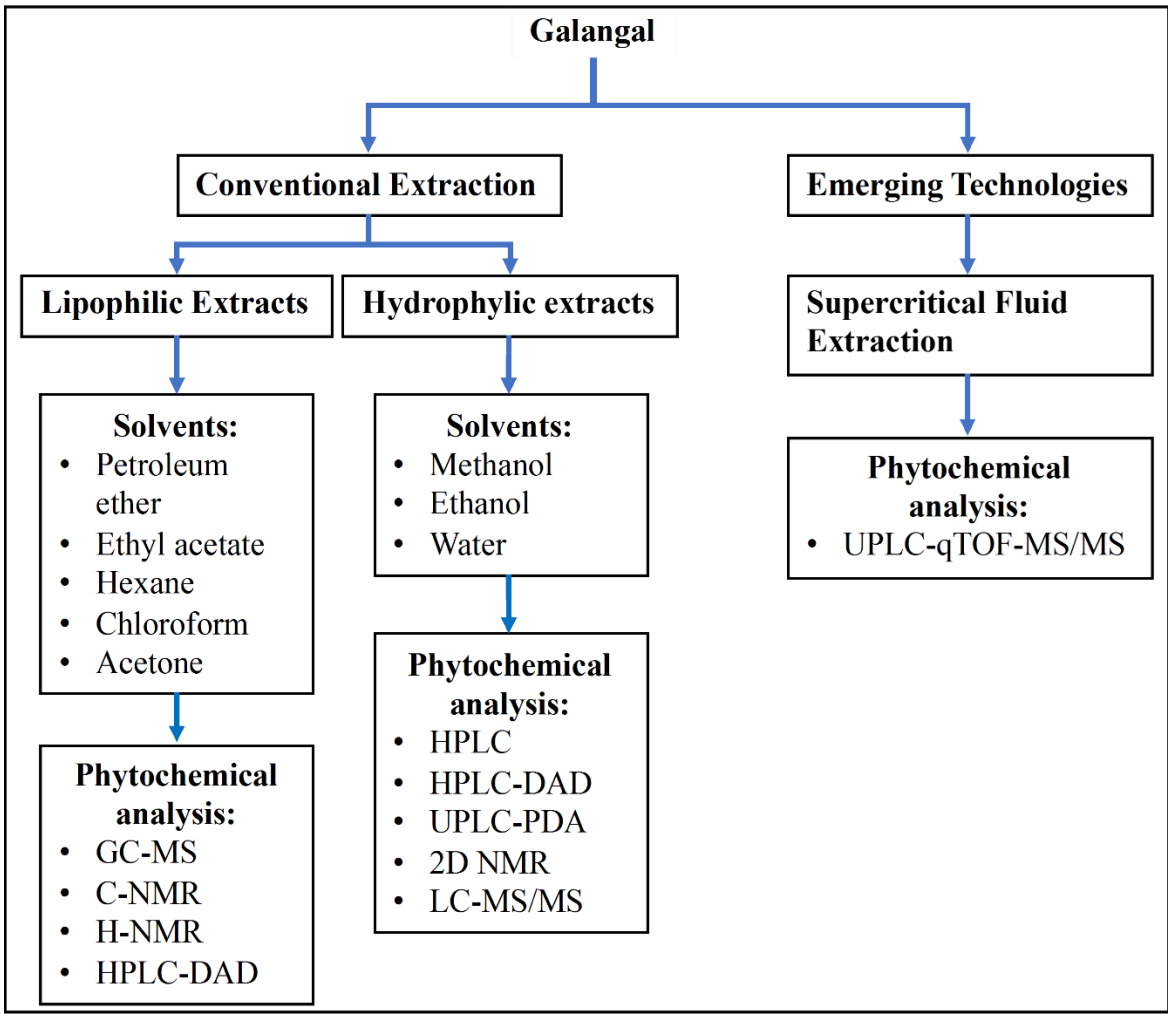

Galangal
Conventional Extraction
Emerging Technologies
Lipophilic Extracts
Hydrophylic extracts
Supercritical Fluid Extraction
Solvents:
• Petroleum ether
• Ethyl acetate
• Hexane
• Chloroform
• Acetone
Solvents:
• Methanol
• Ethanol
• Water
Phytochemical analysis:
• UPLC-qTOF-MS/MS
Phytochemical analysis:
• GC-MS
• C-NMR
• H-NMR
• HPLC-DAD
Phytochemical analysis:
• HPLC
• HPLC-DAD
• UPLC-PDA
• 2D NMR
• LC-MS/MS

Figure 4.

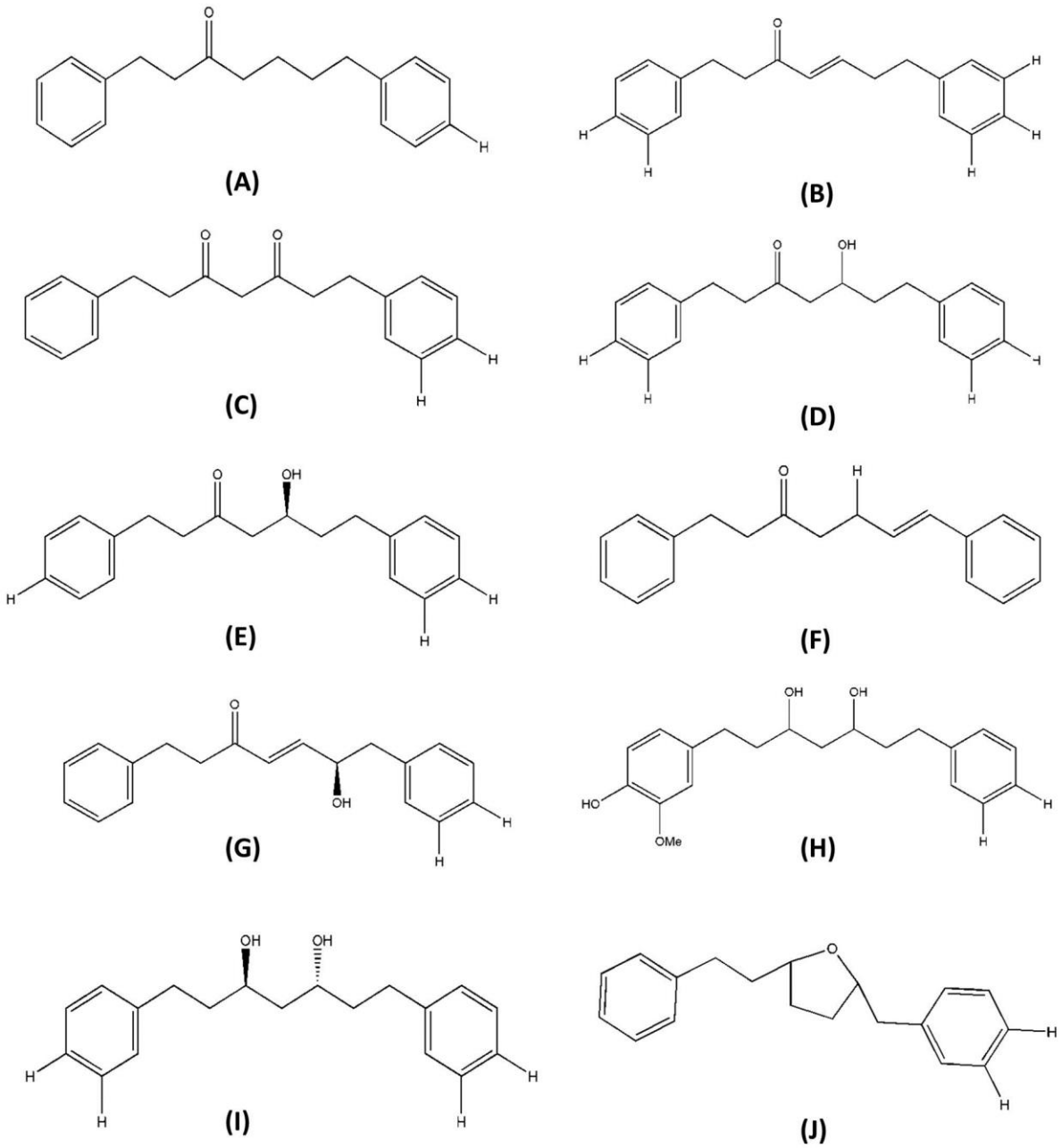
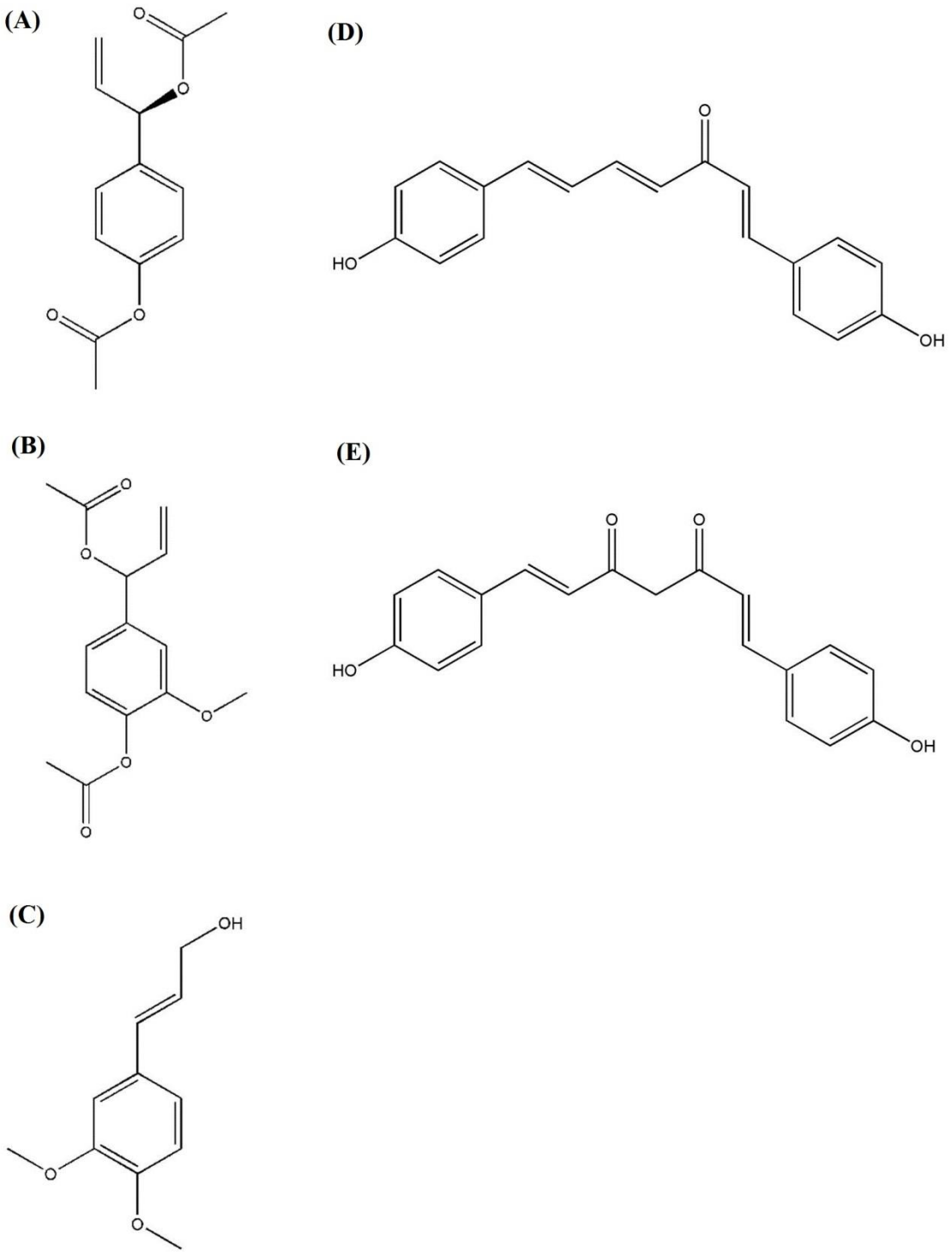


Figure 5.



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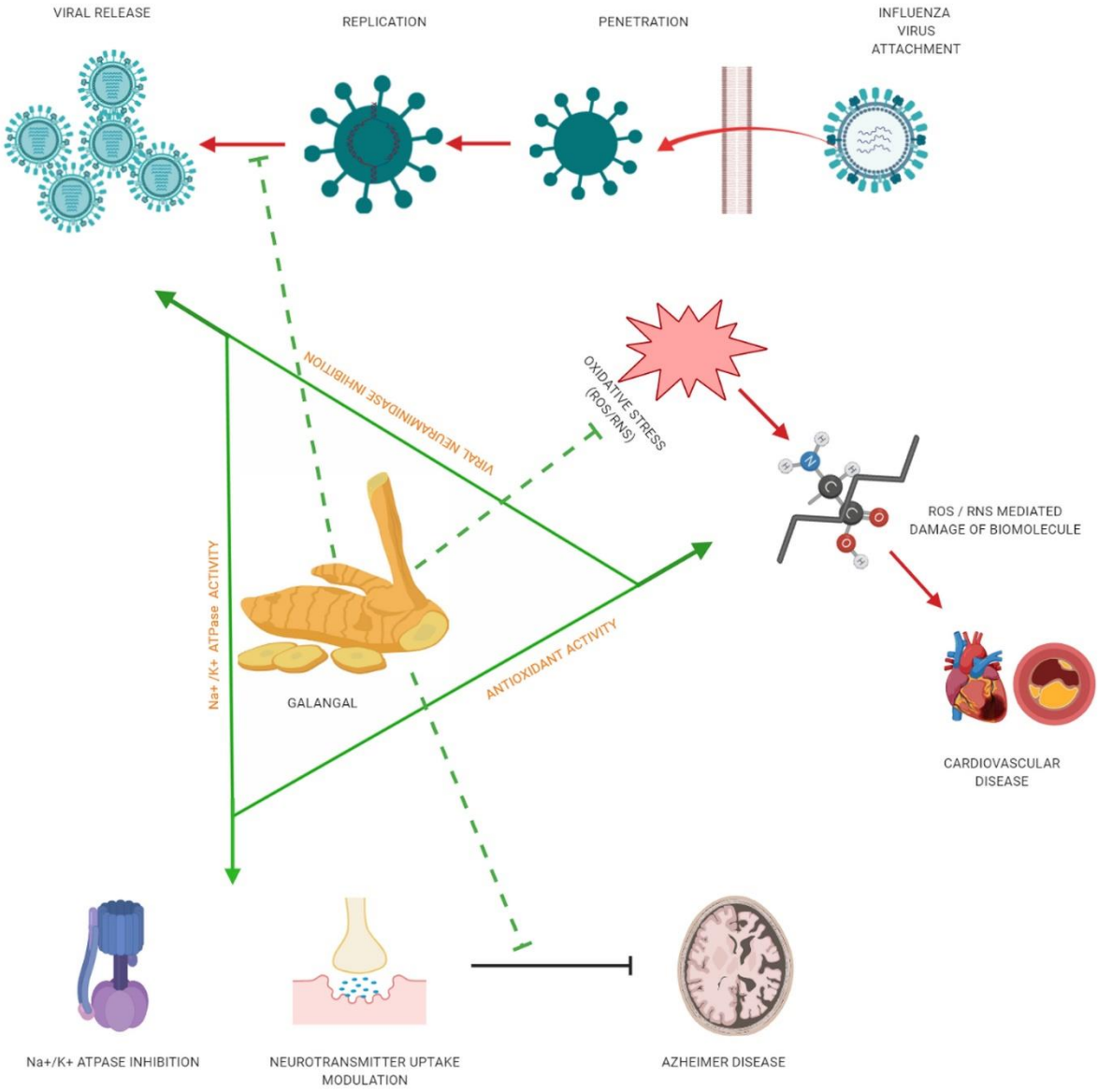
815 **Figure 6.**



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817 **Figure 7.**

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Figure

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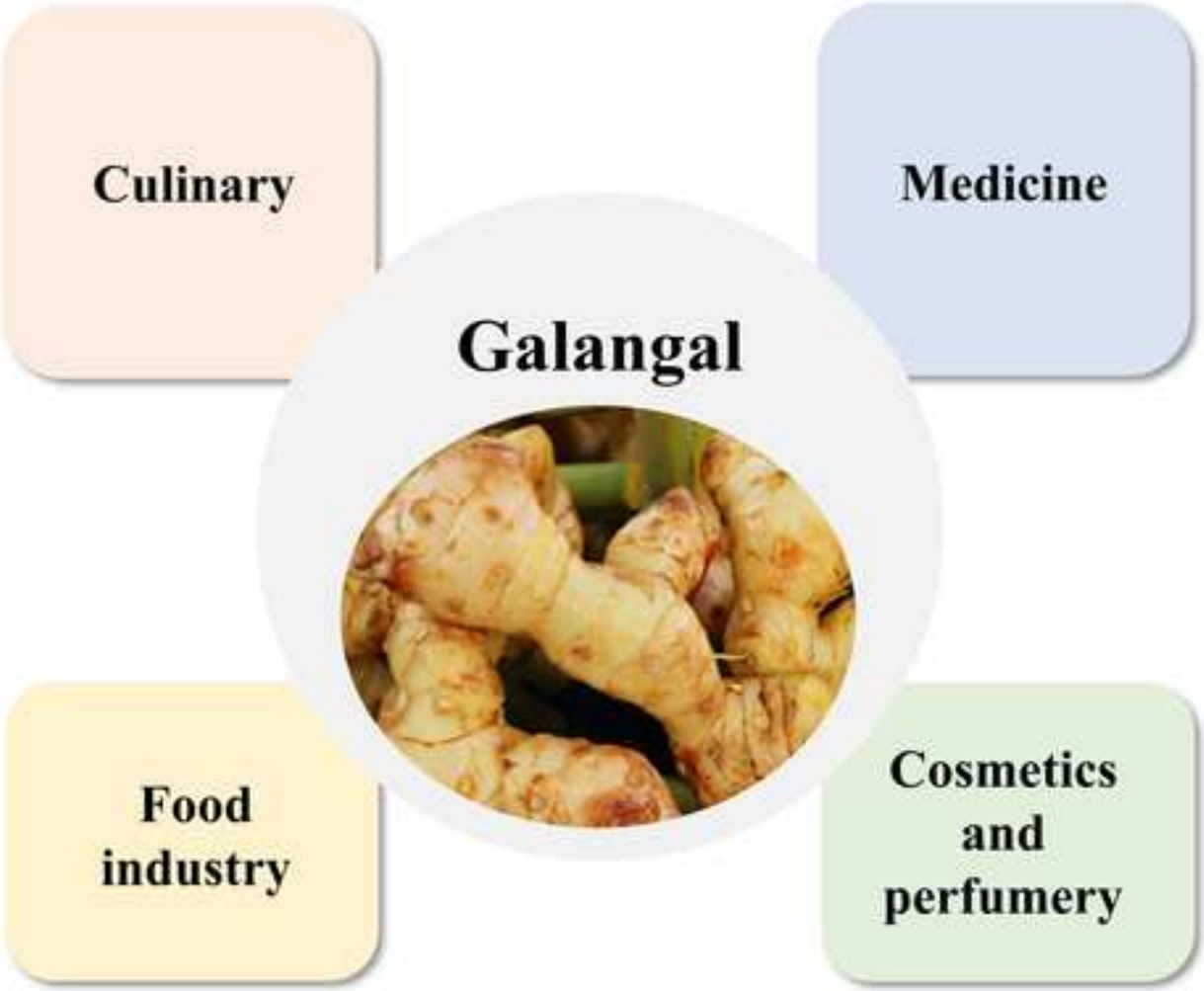

Figure

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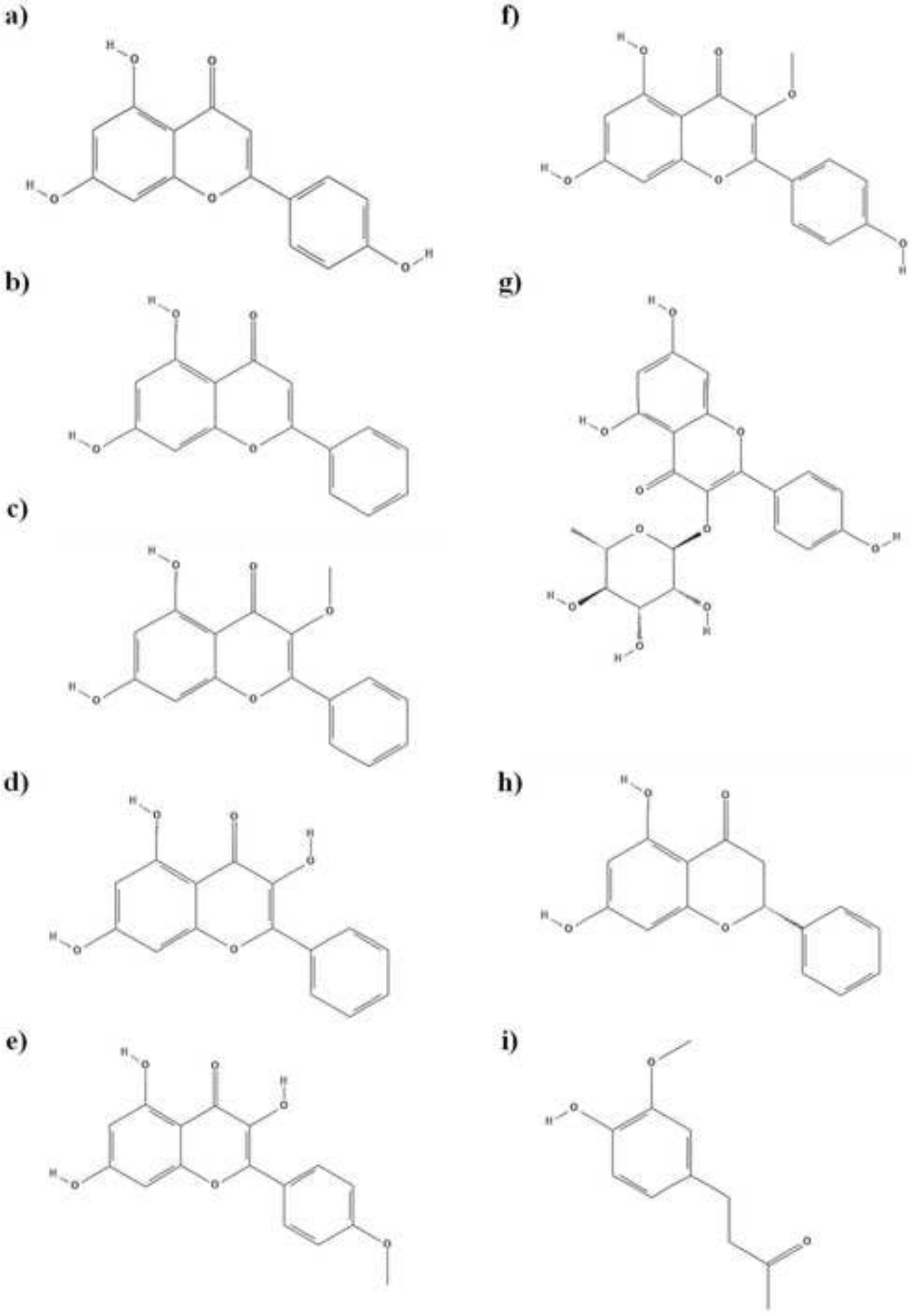

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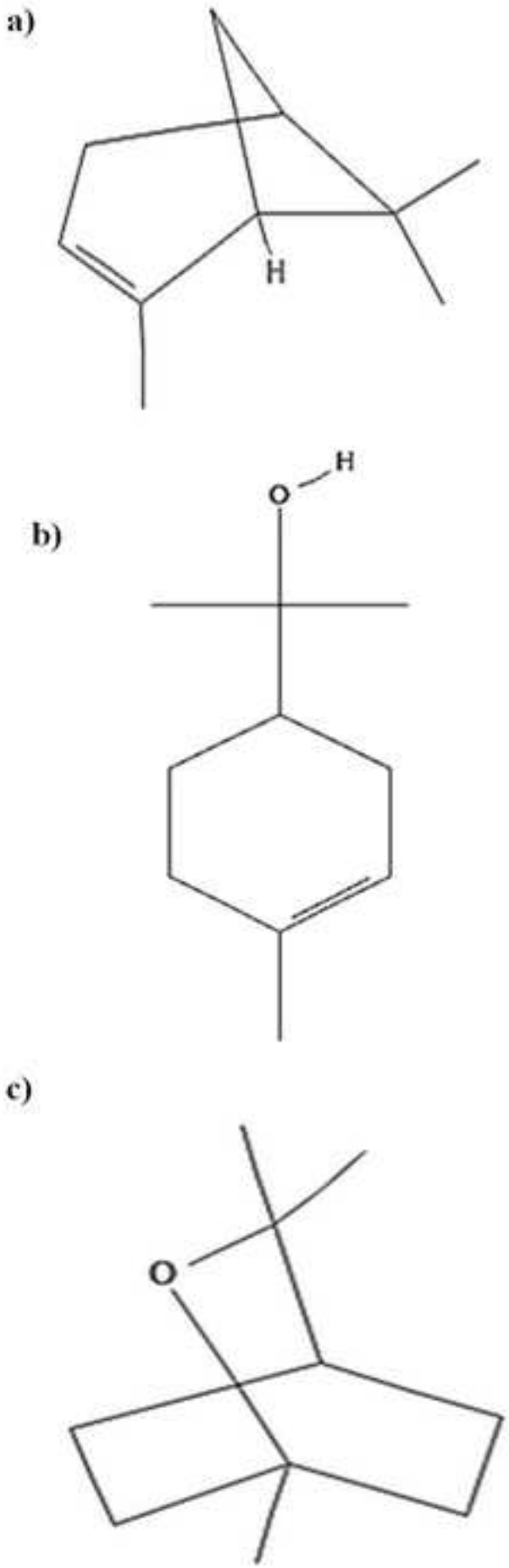

Figure

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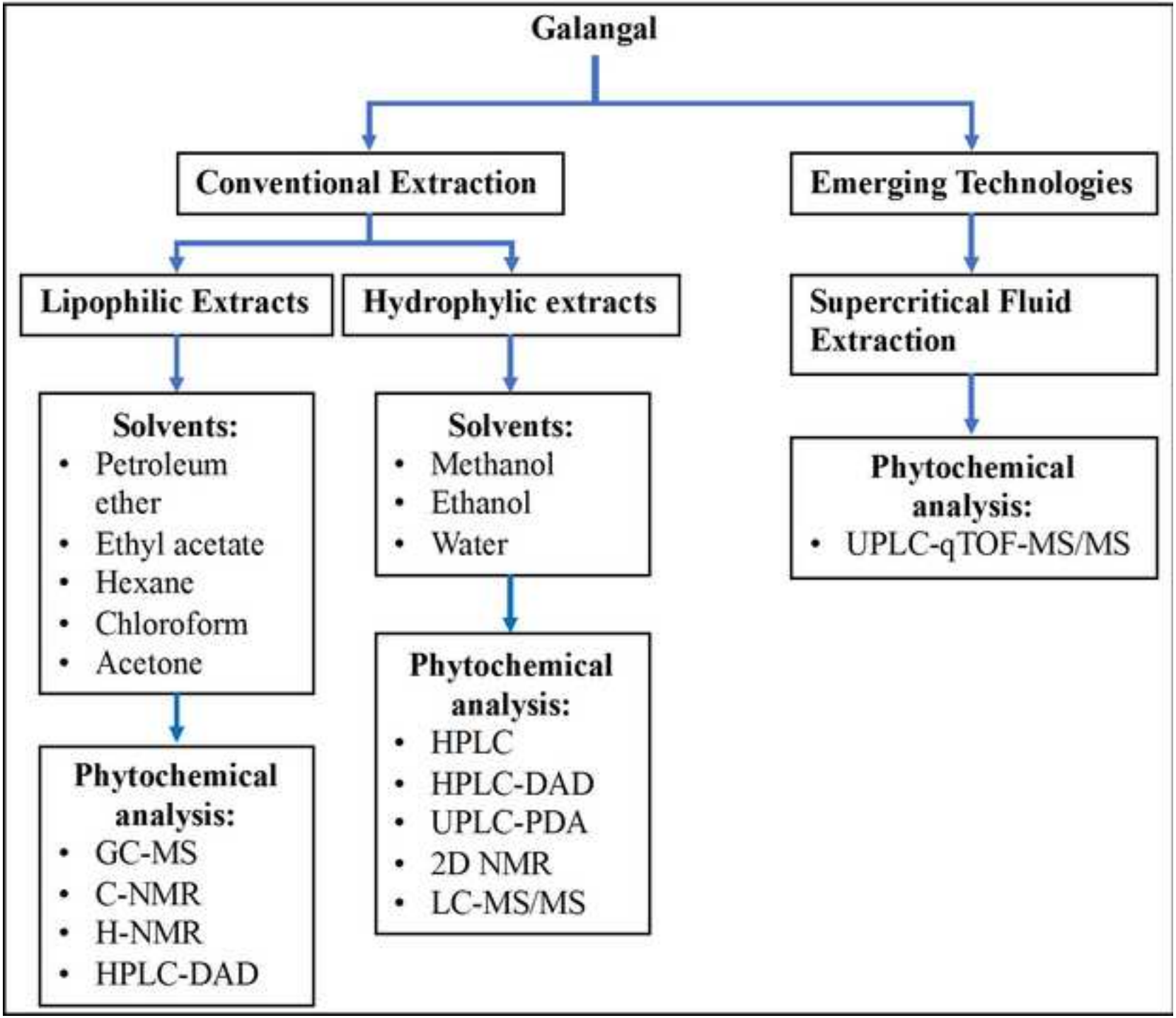

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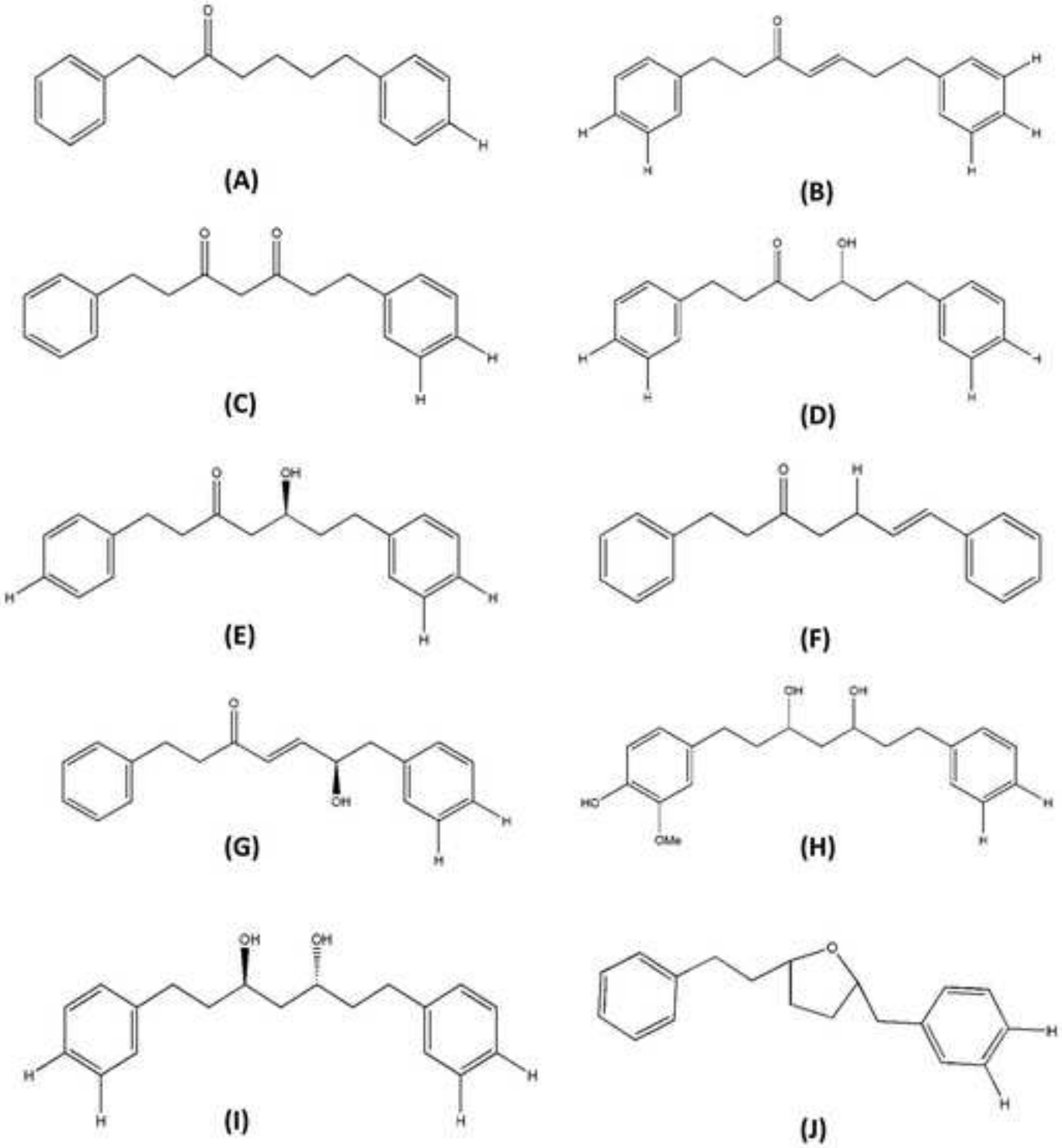

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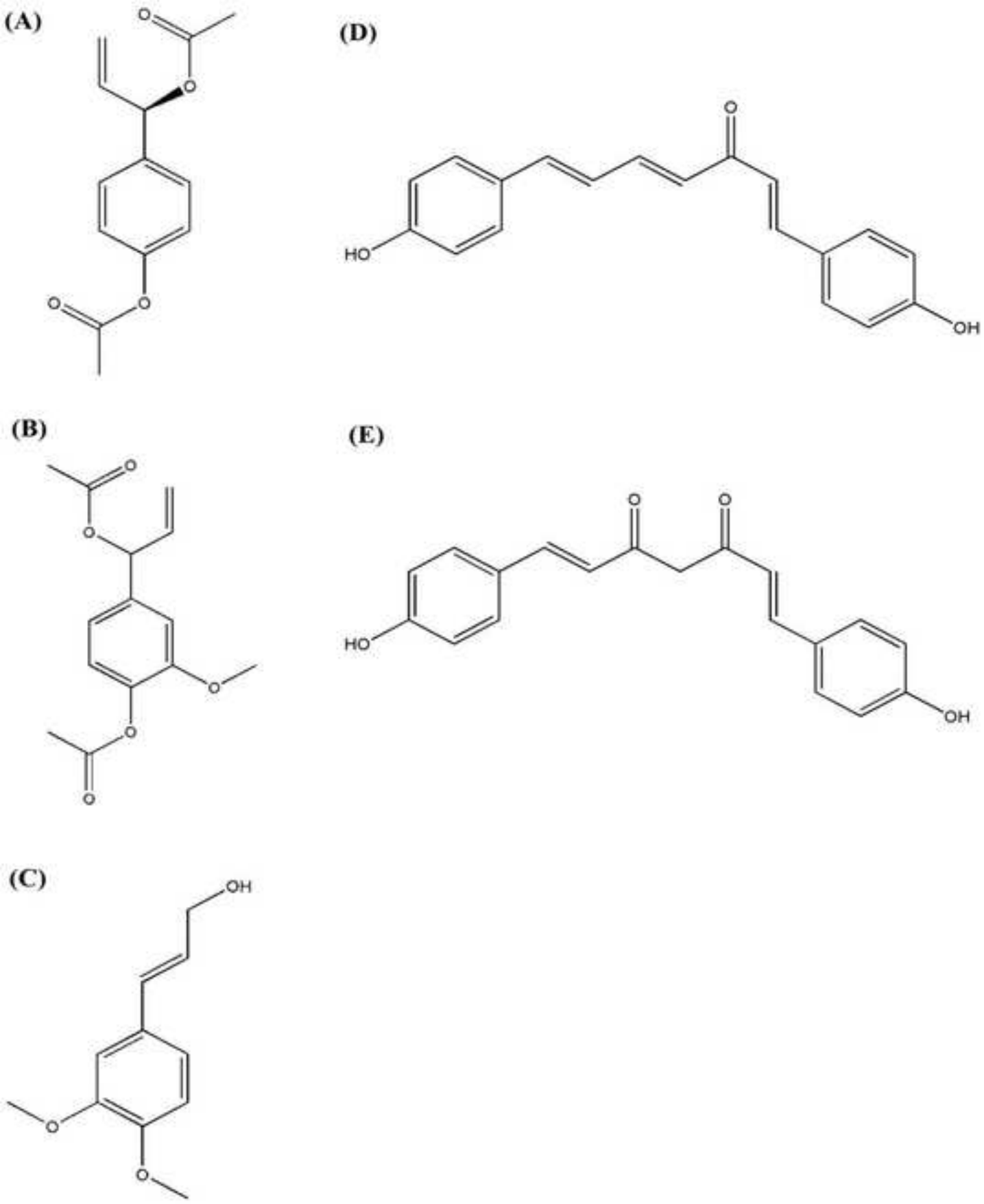

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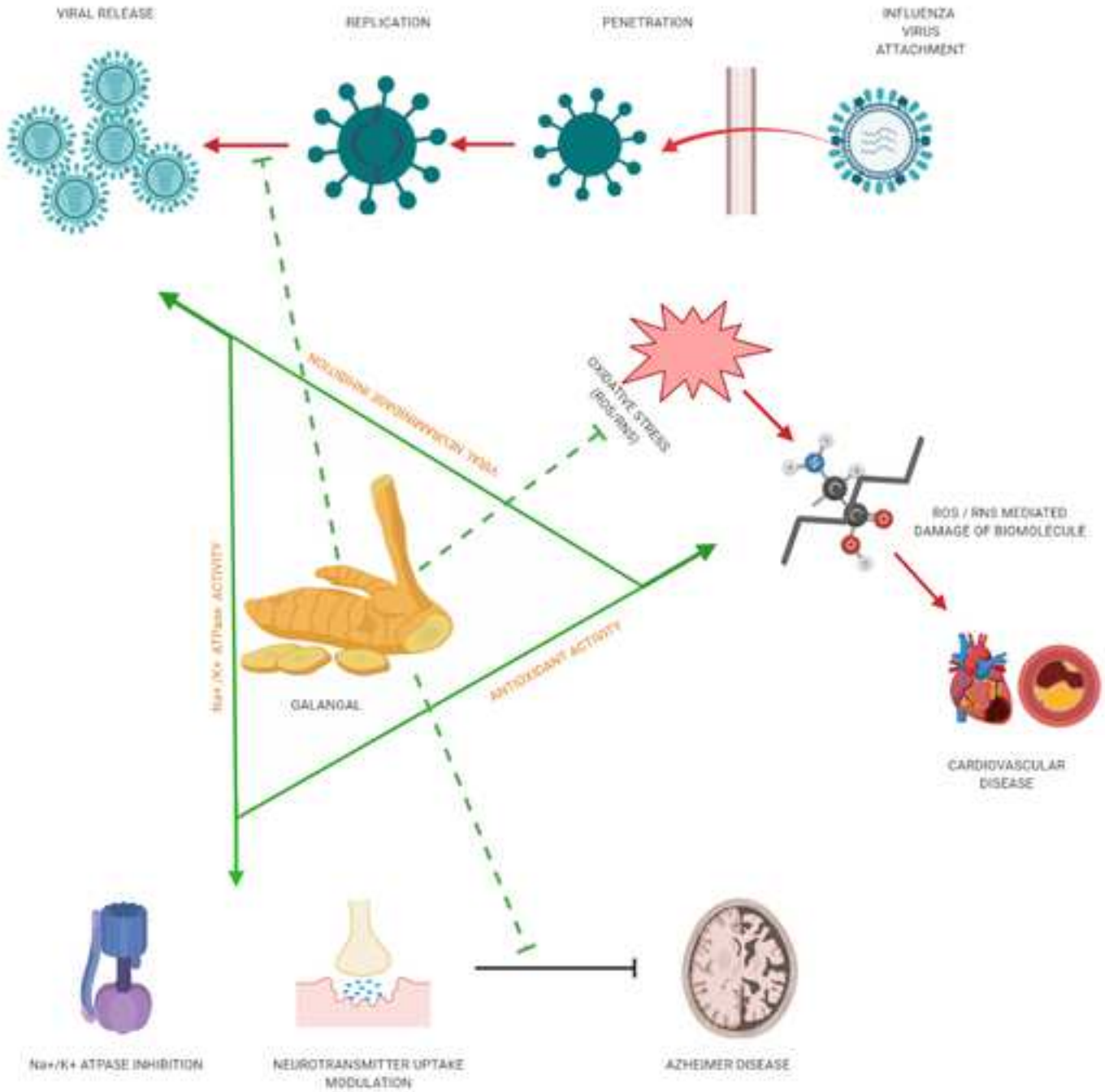

Author statement

Jk Patra and G Das conceptualized the whole concept. JK Patra, G Das, S Goncalves, JB Heredia, AD Talukdar wrote, review and edited the manuscript. A Romano, S Shome HS Shin helped in collection of literature, review and editing of the manuscript. All authors read and approved the manuscript.