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Review article

Guaiazulene and related compounds: A review of current perspective on biomedical applications

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ABSTRACT

Background: Thousands of people worldwide pass away yearly due to neurological disorders, cardiovascular illnesses, cancer, metabolic disorders, and microbial infections. Additionally, a sizable population has also been impacted by hepatotoxicity, ulcers, gastroesophageal reflux disease, and breast fissure. These ailments are likewise steadily increasing along with the increase in life expectancy. Finding innovative therapies to cure and consequently lessen the impact of these ailments is, therefore, a global concern.
Methods and materials: All provided literature on Guaiazulene (GA) and its related compounds were searched using various electronic databases such as PubMed, Google Scholar, Web of Science, Elsevier, Springer, ACS, CNKI, and books *via* the keywords Guaiazulene, *Matricaria chamomilla,* GA-related compounds, and Guaiazulene analogous.
Results: The FDA has approved the bicyclic sesquiterpene GA, commonly referred to as azulon or 1,4-dimethyl-7-isopropylazulene, as a component in cosmetic colorants. The pleiotropic health advantages of GA and related substances, especially their antioxidant and anti-inflammatory effects, attracted a lot of research. Numerous studies have found that GA can help to manage various conditions, including bacterial infections, tumors, immunomodulation, expectorants, diuretics, diaphoresis, ulcers, dermatitis, proliferation, and gastritis. These conditions all involve lipid peroxidation and inflammatory response. In this review, we have covered the biomedical applications of GA. Moreover, we also emphasize the therapeutic potential of guaiazulene derivatives in preclinical and clinical settings, along with their underlying mechanism(s).
Conclusion: GA and its related compounds exhibit therapeutic potential in several diseases. Still, it is necessary to investigate their potential in animal models for various other ailments and establish their safety profile. They might be a good candidate to advance to clinical trials.

1. Introduction

Guaiazulene (GA), a naturally occurring lipid-soluble azulene derivative used in cosmetics, baby skincare, and makeup products, is derived from plants like *Matricaria chamomilla* L., Callis intratropica blue [1], and guaiac wood oil of *Guaiacum officinale* oil. These plants are primarily found in South America's northern coast or the Caribbean region [2, 3]. In 1949, Plattner was the first person who elucidates the chemical

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structure of GA [4]. Chemically GA (1,4-dimethyl-7-propan-2-ylazulene) is a sesquiterpene bicyclic compound substance found as a primary pigment in various soft corals [5]. It has a molecular formula of $C_{15}H_{18}$ with a molecular mass of 198.3 g/mol and a melting point is 31.5 °C. Azulon, vetivazulen, azunol, guajazulene, kessazulen, and azulol are some other names for GA that are frequently used. It is one of the azulene compounds investigated for pharmacological effects in various illnesses in the past 40 years. It has antiseptic, anti-inflammatory, antimicrobial, antioxidant, epithelializing, antimutagenic, immunomodulatory, fungicidal, expectorant [6], diuretic, diaphoretic, demulcent, and bitter stimulant properties [7]. Additionally, it is used to cure gastritis and canker sores [5,8,9]. It is a potent antioxidant that can scavenge hydroxyl radicals and inhibit lipid peroxidation in the rat hepatic microsomal membrane [10]. Its therapeutic safety is ensured by the lethal dose 50 (LD_{50}) found in rats and mice (Table 1).

The pleiotropic effects of GA inspire curiosity about how they might apply to various neurological, cardiovascular, and immunological conditions. This review aims to draw attention to the most recent GA research and its related derivatives used in various pathological diseases. We also discussed the potential molecular mechanism(s) behind their pharmacological effect.

2. Research methodology

The research plan started with a question, "biomedical application of GA and its derivatives." Subsequently, the literature was searched to address the research plan question. In the current manuscript, different biomedical applications of GA and its derivatives were summarized with the fact that they might be potential candidates to treat different pathological conditions. All the literature used in the manuscript were searched using various electronic databases such as PubMed, Google Scholar, Web of Science, Elsevier, Springer, ACS, CNKI, and books using the keywords Guaiazulene, *Matricaria chamomilla,* GA-related compounds, and Guaiazulene analogous. For each GA-related compound, literature was searched with its name, *e.g.*, guaiol. In the current manuscript, only those articles containing either biomedical applications of GA or GA-related compounds were selected.

3. Guaiazulene-related compounds (analogues)

Multiple compounds with similar moieties like GA are present and termed as GA-related compounds or GA-analogues, which are listed in Fig. 1. Their therapeutic potential is summarized in Fig. 2. In the further segment of the review, we will deliberate on some of the most studied GA-related compounds.

3.1. Sodium guaiazulene sulfonate (GAS-Na)

Human gastritis is commonly treated with GAS-Na, a water-soluble GA analogue with wound-healing and anti-inflammatory characteristics [5]. Additionally, it possesses antibacterial, antiseptic, and anti-apoptotic properties. It prevents fMLP-induced leukocyte emigration and histamine production from rodent peritoneal mast cells [11]. At room temperature, GAS-Na is a relatively unstable molecule that progressively breaks down in the solid state. Removal of sulfonic acid results in the formation of stable compound GA (Fig. 3 and Table 2). Chemically, GAS-Na is synthesized by adding sulfonic acid to GA, which is stabilized by freeze-drying or spray-drying aqueous solutions with polymeric additions such as polyvinyl pyrrolidone (PVP) [11].

Table 1
LD_{50} of GA.

Organism	Dose type	Route	Dose	Reference
Rat	LD_{50}	Oral	1550 mg/kg 4 g/kg	[12,13]
		SC	520 mg/kg	
		IP	180 mg/kg	
Mouse	LD_{50}	Oral	1220 mg/kg 3 g/kg	
		IP	525 mg/kg 108 mg/kg	
		IV	56 mg/kg	
		SC	145 mg/kg	

SC: Subcutaneous, IP: Intraperitoneal, IV: Intravenous, LD: Lethal dose.

3.2. Azulene

Azulene is a non-benzenoid or naphthalene isomer and aromatic hydrocarbon compound containing 10 electrons with a fused pentagon and a heptagon ring structure [22]. Azulene has a different color from naphthalene, it has a comparable odor (azulene; dark blue, and naphthalene; white). The name "azulene" is derived from the Spanish word "azul," which means "blue." D. Piesse was the first who discover azulene in 1863, which sparked a great deal of interest in petroleum exploitation. In addition, Plattner and a few other researchers created azulene in 1937 using octahydronaphthalene. In 1942, when Plattner and G. Magyar synthesized it from indane, they published a groundbreaking overview on the production of azulene. Researchers looked into the pharmacological potential of several azulene-based compounds, which are covered in more detail in the further sections of this review [23].

3.3. Guaiene

Guaiene is a naturally occurring terpenoid, derived from various plants like *Bulnesia sarmientoi*. It has the chemical formula $C_{15}H_{24}$ [24,25]. It has been utilized to express tastes, hot scents, and earthy undertones in the flavoring and fragrance industries [26]. Patchouli oil contains various chemical components such as patchouli alcoholic, azulene, seychellene, and guaiene [27]. Guaiene has increased the rat's body and liver weight after being administered a dose of 3135 mg/kg subcutaneously for 7 days [19]. Guaiene has platelet activator factor inhibitory activity; thus, it can provide anti-allergic and anti-inflammatory actions [28]. Guaiene might be a possible therapeutic choice for allergy and inflammatory diseases based on the above data.

3.4. Guaiol

It is also known as champacol. It is an alcoholic organic sesquiterpenoid molecule found in several medicinal plants, including guaiacum and cypress pine [29]. It shows antibacterial and antitumor properties [30,31]. It inhibits cell growth and stimulates double-strand break (DSB)-induced non-small-cell lung cancer (NSCLC) cell death *via* autophagy-arbitrate breakdown of RAD51. It is still unclear what specific mechanism underlies autophagy. But gene ontology (GO) analysis revealed that it is associated with signal transduction pathways by down-regulating soma [32]. Mammalian target of rapamycin (mTOR), a member of the phosphatidylinositol 3-kinase-related kinase (PIKK) family of kinases, has two functional complexes: mTORC1, composed of mTOR, mLST8, Raptor, mSIN1, and PRAS40 [33]. Previous studies have demonstrated that mTOR (P-S2448) and mTORC1 boosted the PI3K/Akt signaling pathway, which in turn promotes the translation of several crucial proteins regulating growth and the cell cycle, including Cyclin D1 and c-Myc, *via* 4E-BP1 phosphorylation (Thr37,46,70, Ser65) and p-AKT (S473) [34]. Guaiol, which has been discovered to be a more powerful mTOR inhibitor than rapamycin, reduces NSCLC cell viability by inhibiting mTOR signaling (Fig. 4) [35]. Guaiol reduces the phosphorylation (Ser2481) of mTOR, reducing AKT's activity (mTORC2 substrates). It further enhances the inhibitory activity of p70 S6K or 4E-BP1 (mTORC1 substrates) and reduces the viability of NSCLC cells [31]. *In vivo* study on mice, guaiol has shown anti-nociception and anti-

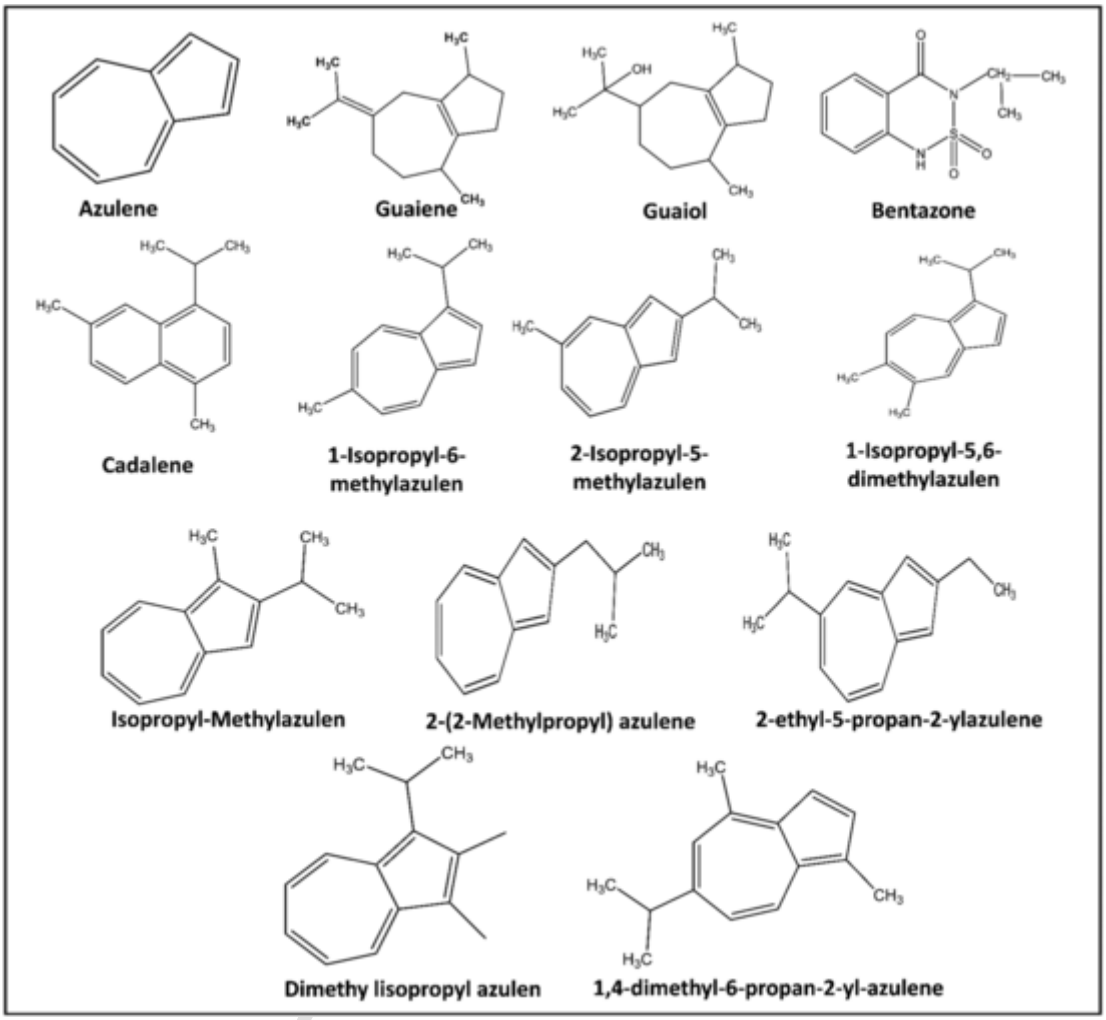

Fig. 1. List of Guaiazulene derivatives.

inflammatory effects at 1, 10, and 30 mg/kg doses by oral administration against acetic acid [18].

3.5. Bentazone (BTZ)

Bentazon is a benzothiadiazine with an isopropyl group replaced at position 3 in the structure 1H-2,1,3-benzothiadiazin-4(3H)-1,2,2-dioxide. It is an herbicide that preferentially kills broadleaf weeds by blocking photosynthesis. Sodium Bentazone is available commercially [36,37] to control the herbaceous plants and shrubs in alfalfa, arugula, cereal grains, clover, digoxin, onions, *etc.* [38,39]. *In vivo* study on mice has confirmed that bentazone does not show any genotoxicity or impair spermatogenesis at a low dose (30 μg/L for 100 days) [20].

3.6. Cadalene

It is a polycyclic aromatic hydrocarbon with $C_{15}H_{18}$ and a cadinene skeleton [40]. It is a sesquiterpene terpenoid found in essential oils [41]. Various other cadalene-like compounds, including simonellite, retene, and ip-iHMN, have also been found in nature [42,43]. It is a flavonoid obtained from the plant *Zelkova serrata Makino*. It has a wide range of biological activities, such as anticancer [44]. However, it has a water solubility problem. To overcome this problem, its prodrug is prepared as glycosylated cadalene for cancer treatment [45]. In the *in vivo* study on mice, cadalene protected lung tumorigenesis at doses (6.25, 25, and 100 mg/kg, orally for 25 weeks) *via* a potent antioxidative effect [46]. *In vivo* xenograft study on mice, cadalene has decreased by 45 % to 10 % tumor size at 100 mg/kg dose by oral administration [45]. All these studies suggest the therapeutic potential of cadalene as a potential anticancer candidate.

The percent yield of Guaiazulene and its derivative from *M. chamomile* and other sources are summarized in Table 3.

3.7. SAR of GA and its derivatives

The modification of the chemical structure of GA could provide the analogs with i) improved physicochemical properties, ii) improved therapeutic efficiency, and iii) expand the therapeutic potential in various disease conditions. For example, GaS-Na, a derivative of GA, has an additional sulfonic group (NaO_3S) that gives their hydrophilic character with additional activities such as antibacterial, antimalarial, antiviral, and antifungal. Adding the sulfonic group at the C-1 position enhances the anti-ulcer activity [57]. The anticancer activity of GA increased when the isopropyl group was added to its seven-membered ring and the amide group was added to its five-membered ring [58]. The positioning of functional groups on guaiazulene derivatives such as 1-isopropyl-6-methylazulen and 2-isopropyl-5-methylazulen might be associated with their tumor-specific cytotoxic action [59]. Azulene is an isomeric compound of naphthalene that consists of two rings, *i.e.*, cycloheptatriene and cyclopentadiene, with 10π electrons. Due to structural similarities to naphthalene, it has a strong antimicrobial activity [60]. Alcohol properties due to the hydroxyl group at the 16th position in the

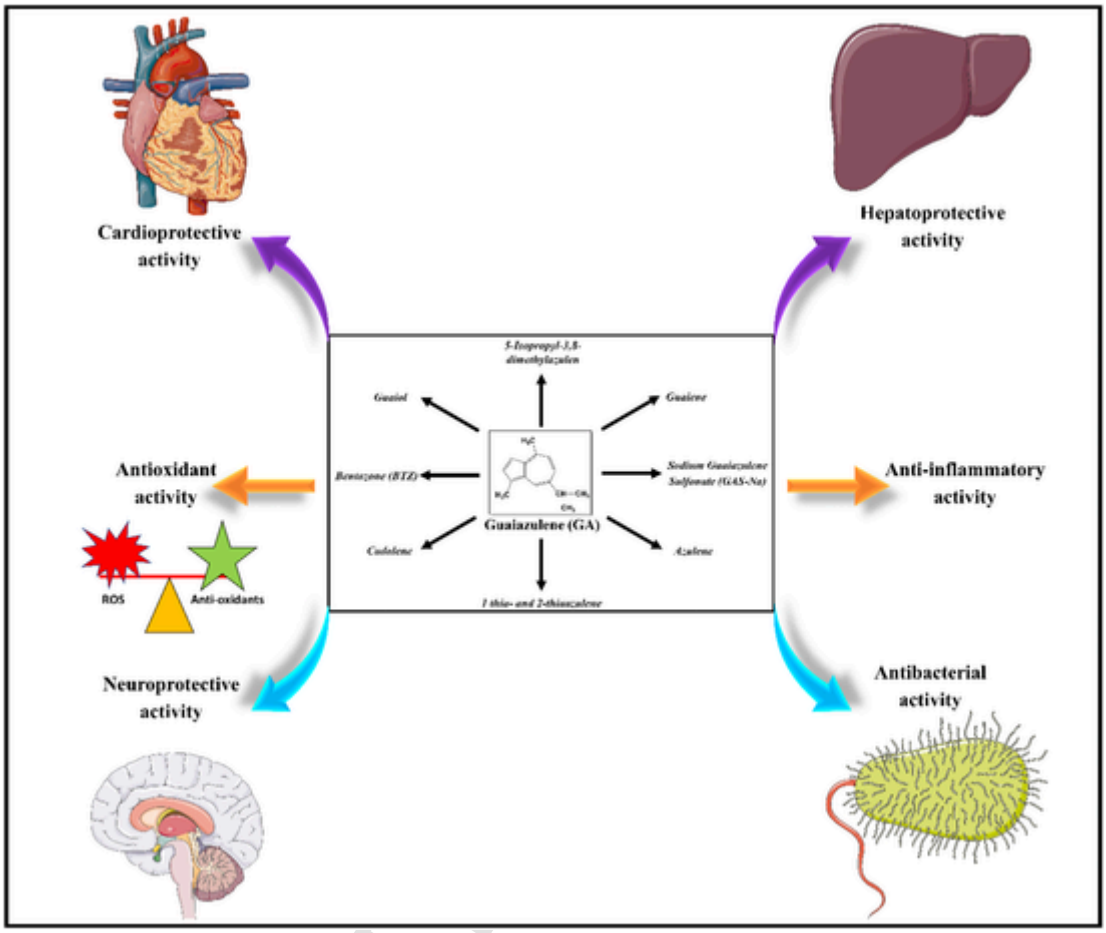

Fig. 2. Therapeutic potential of Guaiazulene-related compounds.

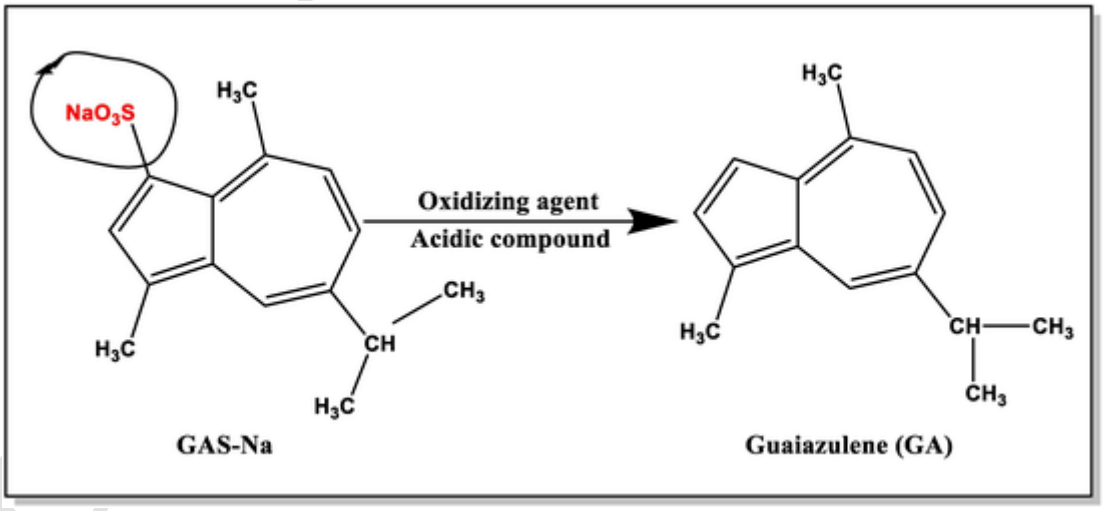

Fig. 3. Synthesis of Guaiazulene from the GAS-Na.

guaiol compound on the exocyclic section of the molecule might be responsible for the antileishmanial activity [53]. Arylamino-substituted GA derivative has more potent anti-gastric ulcer activity than alkylamino-substituted GA derivative compound [57]. Aromatic rings are also responsible for potent anti-gastric ulcer activity due to adding 1-naphthyl amine to GA derivative compound [61]. In bentazone compound, sulfonamide moiety (-SO_2-NH-) at the 8th and 11th positions are responsible for various biological activities such as potent antibacterial, antioxidant, anti-inflammatory, and anticancer [57]. GA and its derivatives, such as cadalene, azulene, GAS-Na, 1-isopropyl-6-methylazulen, and 2-isopropyl-5-methylazulen, have potent antioxidant activities due to their alternate double bond with the conjugated position that permits to scavenge free radicals easily. Their potent antioxidant property also shown hepatoprotective effect (Fig. 5) [62]. There is a need to explore the effects of other modifications on GA and

Table 2
Therapeutic potential of GA and GA-related compounds.

Sl. no.	Drug	Animal	Dose, route, and duration of treatment	Disease model	Pharmacological actions	Outcomes	Reference
1.	Guaiazulene	Rat	Single dose of 250 mg/kg, intraperitoneally	Paracetamol-induced hepatotoxicity	Lipid peroxidation is inhibited *via* the prevention of oxidative stress and increases the level of glutathione	Antioxidant and hepatoprotective effects	[14]
			10 and 50 mg/kg, orally for 5 days	Dextran and histamine-induced edema	Histamine-induced edema was inhibited	Prevent the edema	[15]
		Guinea pig	100 mg/kg, intraperitoneally 1 h. before antigen	Antigen-induced inflammation	Passive cutaneous anaphylaxis reaction was inhibited	Anti-inflammatory effect	
2.	Azulene	Rat	10–200 mg/kg, orally for 3 days	Phenobarbital altered the azulene metabolism	Metabolic enzymes CYP1A2 and CYP2B1 were inhibited	Improved urine color and metabolism	[16]
		Rabbit	100 mg/kg, intramuscularly for 5 days	Burning-induced inflammation	Leukocytosis count was increased	Decreased inflammatory edema, and coagulation of the blood	
3.	Guaiol	Rat	157.5 mg/kg, orally for 3 days	–	–	PK values observed: half-life (9.18 ± 3.75 h), the mean residence time (9.07 ± 3.86 h), the maximum guaiol concentration and time in plasma (28.63 ± 6.82 ng/mL) and (0.50 h)	[17]
		Mice	1, 10, 30 mg/k, orally 1 h. before acetic acid	Acetic acid-induced writhing response	Opioid receptors and adenosine triphosphate-sensitive K^+ channels were inhibited in the presence of guaiol	Antinociception and anti-inflammatory	[18]
4.	Guaiene	Rat	3135 mg/kg, subcutaneously for 7 days	Hepatectomized by surgically	Excrete out the toxins from the *liver*	Increased the weight of the liver and body weight	[19]
5.	Bentazone	Rat/ mice	21 μg/kg/day, orally for 100 days	–	Changed in the timing of the seminiferous epithelium cycle	A low dose does not impair spermatogenesis, but stages of the seminiferous epithelium cycle were altered	[20]
6	Cadalene	Mice	6.25, 25, and 100 mg/kg for 25 weeks	n 4-(methylinitrosamino)-1-(3-pyridyl)-1-butanone (NNK)-induced lung cancer	Increased the expression of the p53 protein and decreased the level of proliferating cell nuclear antigen (PCNA)	Inhibited the lung tumorigenesis	[21]

subsequently access them for their therapeutic benefits over the GA and already developed GA-related compounds.

3.8. Toxicity of GA and its derivatives

Bentazone, a non-toxic derivative of GA, has been proven in acute intoxication studies on sheep. In a study for 84 days, bentazone with sunflower oil (1:5) at doses of 175 mg/kg (1/10th of its LD_{50}) and 97.5 mg/kg (1/12th of its LD_{50}) negatively impacted haemoglobin, leukocyte, and erythrocyte count [63]. *In vivo* study on mice, cadalene derivative has shown antioxidant and chemopreventive effects at 100 mg/kg, orally without any other harmful toxicant effects. However, it has a major problem due to its insolubility in water [45]. Guaiol has shown good insecticidal activity at the concentration of 70 mg/L and good contact activity against insect larvae of *Mythimna separate* and *Plutella xylostella* with LD_{50} of 0.07 and 8.9 mg/larva [64]. Guaiene has potential contact toxicities against cigarettes, red flour beetle, and booklouse with LD_{50} 17.9 μg/adult [65].

3.9. Side effects of GA and its derivatives

Guaiazulene has no systemic and local side effects after locally applied on the skin in diaper dermatitis [66]. *In vitro* study of GA on phototoxic features and cytotoxicity has shown no harmful adverse effects [67]. However, minor side effects, such as allergic contact cheilitis, were seen after using guaiazulene-containing toothpaste [68]. A study on bentazone has confirmed that it is non-toxic in honeybees and beetles [37]. However, it causes allergic side effects, such as skin, eyes, and respiratory tract irritation. It also shows severe side effects such as acute renal and respiratory failure on large doses [69]. Guaiol has no side effects due to its non-irritating, non-toxic, and non-sensitizing properties [70]. Guaiene has no specific side effect but increases body weight on higher doses [19].

4. Potential biomedical applications of guaiazulene and GA-related compounds

Researchers are looking into the potential pharmaceutical and biological uses of Guaiazulene and GA-related chemicals, including their anti-inflammatory, ulcer-protective, anti-neoplastic, hypoglycemic, antiviral, antibacterial, fungicidal, and antioxidant activity [71–73]. The further section of the review discusses the therapeutic potential of GA and GA-related compounds in detail.

4.1. Hepatoprotective

The tricarboxylic acid (TCA) cycle and ATP generation are two metabolic processes dependent on mitochondria, which are prevalent in hepatocytes and provide energy to the liver and other body parts. Numerous studies have shown the importance of mitochondria in hepatocytes as a key mediator in hepatotoxicity due to environmental pollutants [74]. It was recently discovered that COVID-19-liver damage is associated with greater mortality and ICU admission rates. A recent study with 1100 participants found that 18 % and 56 % of COVID-19 patients with non-severe and severe disease, respectively, had high blood aspartate transaminase levels (AST) [75,76]. Throughout the COVID-19 infection, several therapies, including antipyretics (such as paracetamol), antibiotics, antivirals, and other synthetic pharmaceuticals, also caused liver damage [77]. As the prevalence of liver disease rises steadily, new therapies must be developed to avoid the hepatotoxicity of synthetic medications. Herbal medications are the most appropriate in this situation. In molecular coalitions, GA and GA-related molecules provide promising new opportunities for hepatoprotective treatment.

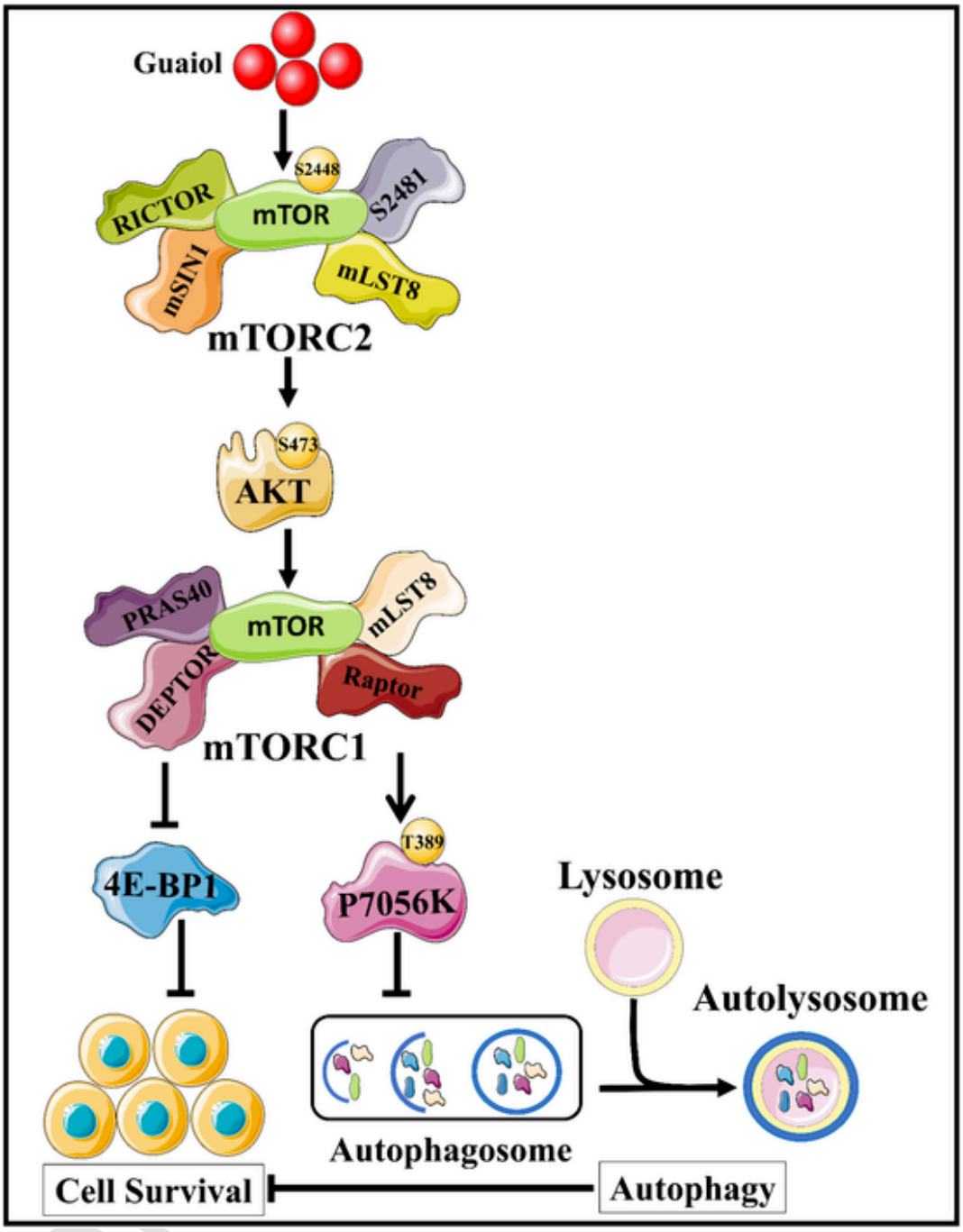

Fig. 4. Mechanism of Guaiol in NSCLC.

GA neutralized 2,2-diphenylpicrylhydrazyl (DPPH) and hydroxyl radicals in the rat liver and prevented lipid peroxidation [78,79]. The liver's CYP450 enzymes metabolize paracetamol (PCM) and transform it into the active metabolite *N*-acetyl-p-benzoquinone imine (NAPQI), which leads to GSH depletion in a dosage-dependent manner (GSH) [80], which subsequently breaks and detoxifies NAPQI. Due to the depletion of GSH, NAPQI interacts with the sulfhydryl group on proteins to generate the protein complex 3-(cysteine-S-yl)-acetaminophen (APAP-Cys) [81]. This adduct is linked to liver toxicity (necrosis). GA may have a potential chain-breaking antioxidant activity that stops lipid peroxidation and shields the liver from paracetamol's hepatotoxic effects [11]. It guards against paracetamol toxicity, blocks the activity of numerous CYP450s, and inhibits NAPQI-induced GSH depletion [10, 82]. These characteristics point to the possible therapeutic uses of GA in other hepatotoxic diseases.

4.2. Ulceroprotective

A peptic ulcer is a common condition where sores form in the lining of the stomach that affects 4 % of the population and 10 % of people at some point in their lives [83]. The first-line therapy for treating peptic ulcers is proton pump inhibitors (PPIs), such as omeprazole and pantoprazole. Although PPIs are the most efficient drugs for lowering stomach acid production, but they also have several side effects. Novel anti-ulcer drugs are therefore required. In this situation, the best way to reduce or eliminate the negative effects of synthetic anti-ulcer medications is to use GA and GA-related chemicals as herbal medicines. Cao et

Table 3
GA and its related compounds from *M. chamomile* and other sources.

Sl. no.	Compound name	Sources and percentage (%)	Therapeutic potential	References
1.	Guaiazulene (*M. chamomile)*	Dried flower: (12.42 %)	Antioxidant, Anticancer	[47]
		Dried flower: (25.6 %)	Antimicrobial	[48]
	Guaiazulene (*Euplexaura erecta*)	Whole part: (0.2 %)	Antifungal Antibacterial	[49]
	Guaiazulene (*Pachyclavularia violacea*)	Soft coral: (0.4 %)	–	[50]
2.	Azulene (*Matricaria chamomile)*	Dried flower: (1–15 %)	Antioxidant, Anti-inflammatory, anticancer, anti-allergic, and neuroprotective	[51,52]
3.	Guaiol (*Bulnesia sarmientoi*)	Bark: (48.29 %)	Anti-leishmanial activity	[53]
	Guaiol (*Myroxylon peruiferum*)	Bark: (9.35 %)	Anti-leishmanial activity	
4.	Cadalene *(Cinnamomum cassia)*	Bark: (0.23–0.66 %).	Antifungal activity	[54,55]
	Cadalene *(Myrcia sylvatica)*	Leaves: (4.7–8.2 %) Aerial parts: (6.24 %) Aerial parts: (9.36 %)	Antioxidant Neuroprotective	[56]

al., [5] explored the ulceroprotective effect of GA derivatives *in-vivo* and reported that the synthesis of guaiazulene sulfonate compounds has a dual sulphonyl amino pattern that provides ulceroprotective effects in the alcohol-induced gastric ulcer model [5]. Azulenes have been shown in animal models to exhibit anti-inflammatory, antioxidant, and anti-edema effects, as well as to enhance mucosal blood flow, decrease histamine levels, and consequently secrete less stomach acid [84,85]. GA mildly induces mucous membrane irritation after patch-checking on inflamed lips [86]. Guaiazulene and GA-related compounds are naphthalene isomers whose chemical properties differ from naphthalene isomers. Similar to GA, several related compounds have been investigated for their pharmacological and therapeutic properties, including their ability to block TXA2/PGH2 receptors, decrease stomach acid output, prevent duodenal ulcers [87], improve gastric mucosal blood flow, and inhibit TXA2/PGH2 receptors. Additionally, they were found to have local anaesthetic, anticancer, and antiallergenic properties and to prevent TXA2-induced mortality [88]. For the comparison with PPIs, more research is necessary.

4.3. Diaper dermatitis

During nursing, guaiazulene-containing ointments are routinely used to the breasts. In non-breastfeeding women, it is thought that applying GA to the nipple and areola area may provide benefits (increasing sensitivity and suppleness, safeguarding against wear, cracking, infection, and discomfort) [82]. In research with 20 patients, topical pomade containing GA (0.05 g/100 g) produced favourable results and prompt healing in recalcitrant diaper dermatitis in newborn babies. When compared to standard treatment, its positive and immediate effects were noticeable on the 1st and 3rd days [89]. This local pomade with GA stops the skin from drying out, lessens inflammation, strengthens the stratum corneum epithelium, and shields users from skin irritants [90]. Additionally, it can treat canker sores or gastritis [91]. The development of some cosmetic preparations and GA-based formulations to treat various skin-related conditions should be worthwhile in light of the aforementioned facts.

4.4. Anti-cancer

With 18 million new cases and 9 million fatalities from cancer or other malignancies recorded globally in 2018, cancer or other malignancies continue to pose a serious health risk. Despite the broad availability of anti-neoplastic drugs, cancer remains one of the leading causes of death globally. There is a need to develop or repurpose novel therapies to treat cancer patients as the illness burden keeps rising [92,93]. Several natural compounds are investigated for their anti-cancer activities [94]. The GA and its related compounds raise hopes for new anticancer treatments as a part of molecular consortia. Chamazulene,

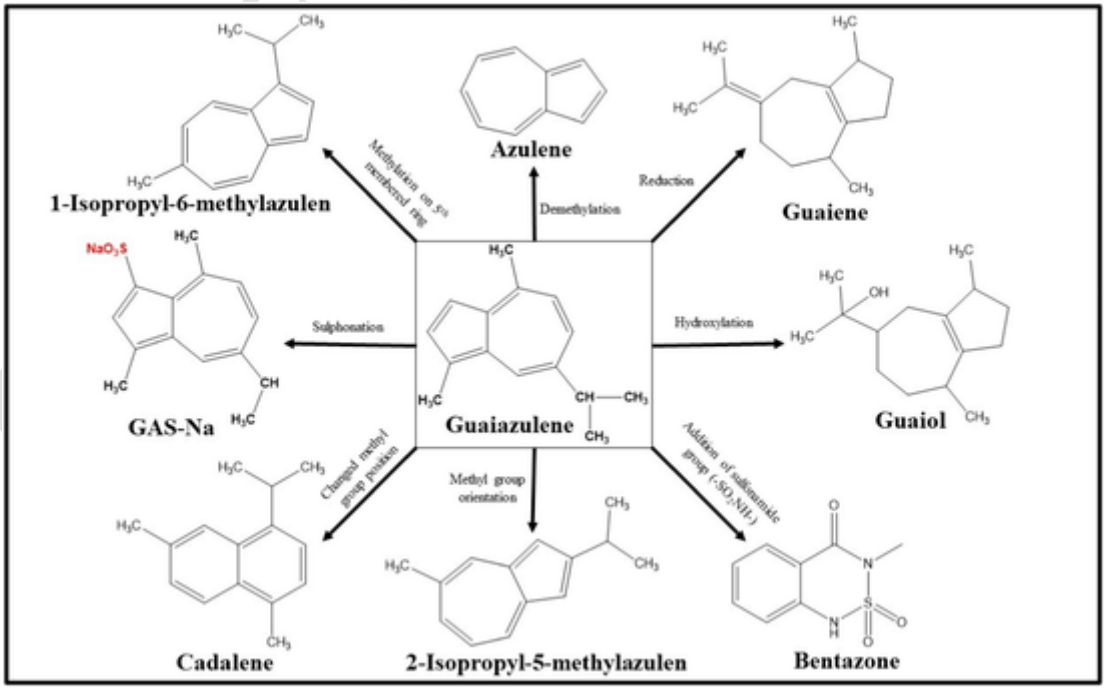

Fig. 5. Different modifications on Guaiazulene.

extracted from the leaves of Artemisia arborescent and containing 63 % GA, showed favourable apoptosis-inducing effects on cancer cells [95]. According to other studies, chamazulene is a more potent antioxidant than ascorbic and tocopherol. GA inhibited neuronal and N2a neuroblastoma (N2a-NB) cell proliferation while increasing and decreasing free radicals and antioxidant markers levels, respectively [96]. *In vitro,* GA showed cytotoxicity on N2a-NB and rat neuronal cells. However, the cytotoxicity of GA on healthy neuron cells and its poor treatment absorption in N2a-NB cells limit its effectiveness as an anticancer chemotherapeutic [97]. In addition to GA, other sesquiterpenes compounds, such as transfarnesol, cis-nerolidol, and alpha-humulene, also demonstrated antiproliferative effects *in vitro* on Caco-2 cell models.

In vitro studies demonstrated that GA has antitumor activity against NSCLC cells, mediated by mitochondrial malfunction, oxidative stress generation, and mitochondrial ATP depletion, which results in anoikic cell death [98]. Concurrently, GA also induced autophagy and inhibited Akt/mTOR pathway in NSCLC cells (Fig. 6). Co-administration of GA with paclitaxel amplified its antitumor effect. Furthermore, *In vitro* study demonstrated that GA treatment reduced the level of proteins like integrin-3 and Akt phosphorylation at A549 and H1975 cells (NSCLC cell line) [99]. Alkoxyl guaiazulene-3-carboxylates have recently been proposed as a lead molecule for the new anticancer medicine. The anticancer action of the GA derivative guaiazulene-3-carboxylate against oral cancer cells has been established [58]. It's also important to investigate GA's anti-tumorigenic effects on different cancers. It might prove to be an effective anticancer medication.

4.5. Antimicrobial

One of the biggest achievements of humanity in medicine is the discovery of antibiotics, which happened about 100 years ago. Due to an increase in bacterial resistance, antibiotics have lost some of their effectiveness recently [72]. Therefore, it is necessary to investigate potential new antibacterial and antiviral medication options. There is a lot of promise for GA and other azulene derivatives to offer new perspectives on overcoming resistance. They can be used in antimicrobial photodynamic therapy because of their phototoxic properties. Xia et al. reported that they could generate free radicals (singlet oxygen) after UVA luminous excitation [100]. Damrongrungruang et al. [101] showed azulene's effect on the viability and generation of singlet oxygen in peripheral blood mononuclear cells (PBMCs) *in vitro*. They discovered that azulene at concentrations of 5–500 μM produced singlet oxygen when triggered with a light-emitting diode at 625 nm. The proposed mechanism involves ROS production that destroys intercellular components, particularly DNA [101]. In the antimicrobial photodynamic therapy (PACT) trial, azulene as a photosensitizer in photodynamic therapy (PDT) reduces microbial *(Streptococcus beta-haemolyticus Prevotella sp. and Fusobacterium sp.)* clearance in ligature-induced periimplantitis in dogs similar to standard treatment.

They also discovered that azulene is useless in the absence of light exposure, suggesting that photodynamic mechanisms are responsible for azulene's antibacterial effects. There was no significant variation among the treatment groups, indicating that photodynamic therapy is a noninvasive strategy for reducing bacteria in periimplantitis [102]. In another study, Dentin plates were contaminated by *Streptococcus mutans* solution. The 1.5 W laser irradiation at 940 nm gave the greatest

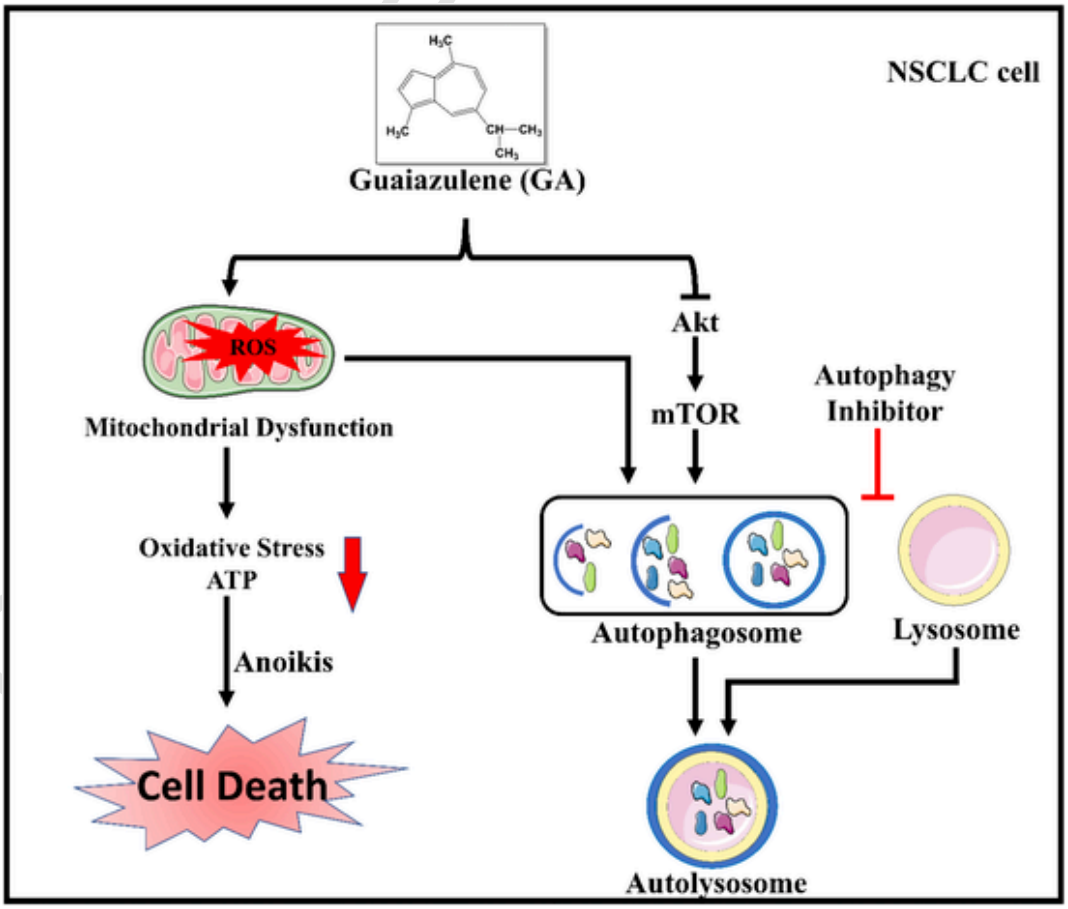

Fig. 6. The mechanism of GA therapy in combination with autophagy suppression in NSCLC. GA leads to mitochondrial dysfunction and subsequently increases ROS, which results in anoikis; meanwhile, it also blocks the Akt/mTOR axis and induces autophagy.

bactericidal activity outcomes by decreasing the colony-forming unit (CFU/ml) [103]. GA showed antibacterial activity against several strains of *M. hominis*. *In vitro* comparative antibacterial activity of GA was evaluated with several natural compounds such as cinnamon oil, linoleic, carvacrol, and eugenol against the *M. hominis* strain and was demonstrated to be efficient against *M. hominis* bacterial strain with the lowest MIC (62.5–4000 s μg/mL) which inhibits metabolism and growth of bacteria in 90 % of tested strains [104]. GA produced from *Euplexaura erecta* demonstrated a negligible antibacterial impact on *Pseudomonas aeruginosa* [105].

4.6. Anti-inflammatory

Inflammation is a natural response to stressors such as tissue damage, wounds, bruises, cancer, and joint issues. However, while inflammation becomes prolonged, the NSAIDs (COX inhibitor) and corticosteroids (immunomodulator) can damage the tissue revert. Unfortunately, they have several adverse effects that necessitate developing cutting-edge approaches to treat chronic inflammation [106]. Guaiazulene and GA-related compounds containing traditional plants, including *Matricaria chamomilla* L. containing camomile and *Achillea millefolium*, have demonstrated anti-inflammatory activity. A camomile extract called sulindac specifically suppressed COX-2. The study suggests chamazulene efficiently reduces inflammation in the rat model of osteoarthritis produced by Freund's adjuvant [107]. GA and other chamazulene derivatives have powerful antioxidant and anti-inflammatory activities while being non-toxic [84,108]. In PBMC and fibroblast (FB) cells, photodynamic treatment utilizing GA that was exposed to a 635 nm red laser pointer reduced inflammation without resulting in cell death [109]. GA that had been given a 4–8 J/cm^2 dose of radiation produced singlet oxygen (O_2) expressed normal T cells and secreted RANTES and prostaglandin E2 (PGE2) [101,110]. Due to its greater lipophilicity, GA has more cell penetration [111], which is related to its greater anti-inflammation effectiveness [112].

4.7. Mutagenic action

Guaiazulene has numerous biological effects, including cytotoxicity, anti-spasmodic, anti-inflammatory, and antimicrobial. It caused a cytotoxic effect on human peripheral blood lymphocytes (PBLs) at different concentrations (0–400 μg/ml). GA and its derivatives showed cytotoxic activity in cell lines, including gingival fibroblast of humans, human periodontal ligament fibroblast (HPLF), pulp cell, and tumor cell lines of the human, including submandibular gland cell line (HSG), oral squamous cell line (HSC-2, HSC-3), and promyelocytic blood cancer cell line (HL-60) [97]. GA and other derivatives are toxic to human tumors and normal human cells. Azulene and GA showed photo mutagenic characteristics in *Salmonella typhi* bacterial strains, possibly due to photoreactivity.

In contrast, only azulene damaged DNA in Jurkat T-cells of humans. After being exposed to UVA radiation, GA and azulene showed 4 to 5 times higher mutagenicity in *S. typhimurium* TA98, TA100, and TA102 [4]. However, GA and azulene are not mutagenic when tested without light. As exposure to sunlight is unavoidable, caution must be exercised when using Guaiazulene or azulene as ingredients in skin cosmetics [16]. GA and azulene are photolabile in healthcare products. After being applied to the skin, GA is photo exposed and displays an immediate toxic reaction as a result of phototoxicity [113]. Due to the phototoxicity of GA, Azulene could be used in radiation therapy to kill cancerous cells. It is hypothesised that azulene photoirradiation by UVA causes the production of ROS and lipid peroxidation (Fig. 7).

4.8. Antioxidants

A GA derivate 3-Vinylguaiazulene had antioxidant activity measured by 2,2-diphenyl-1-picrylhydrazyl (DPPH) [3]. GA is a naturally occurring, non-toxic chemical with anti-ulcer and anti-inflammatory activities. The rat liver scavenges hydroxyl radicals and DPPH and inhibits lipid peroxidation [14]. In *in vitro* research, GA efficiently inhibits lipids peroxidation in the membranes of microsomal cells [114]. Compared to readily accessible conventional antioxidants like quercetin and propyl gallate, the IC_{50} value of GA is outstanding. GA inhibits membrane lipid peroxidation by scavenging the proxy1 or alkoxyl intermediate radicals to its isopropyl group's allylic hydrogen atom at position 7 and preventing allylic hydrogen abstraction from lipids [86,115]. The attacking radical isolated the hydrogen atom, but the resonant frequency could stabilize the derived GA radical with the benzene ring moiety, which is less responsive [116]. Greater lipophilic-

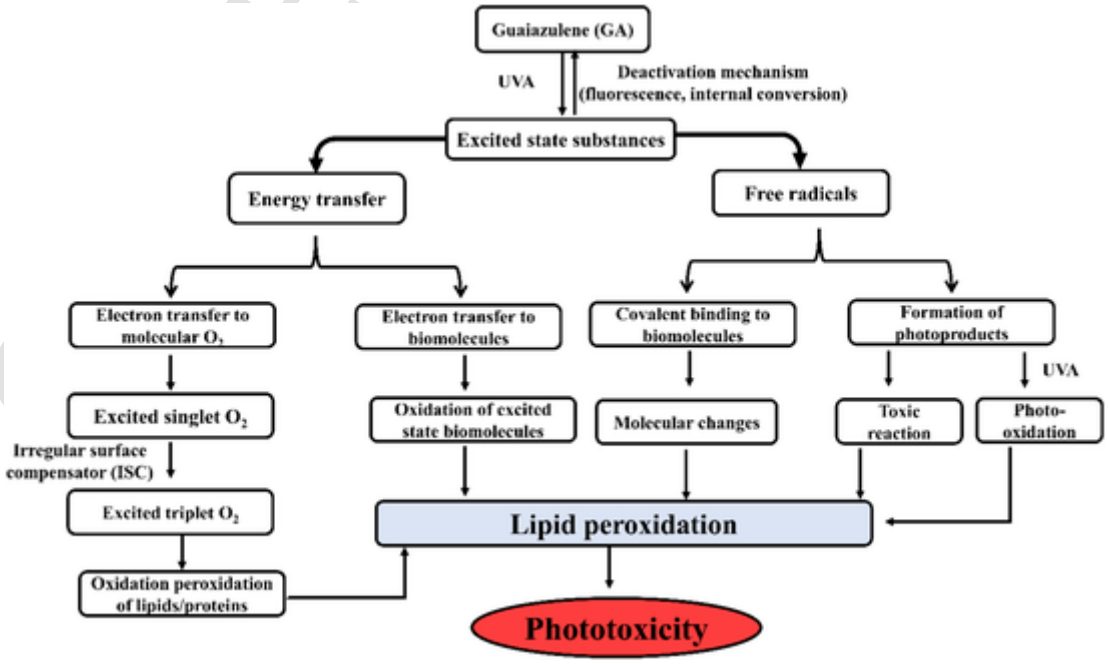

Fig. 7. Possible mechanism for azulene or GA-induced lipid peroxidation and linked responses when exposed to UVA.

ity of GA (conceptual cLogP value of 5.74) is needed to increase its accessibility, interaction, and retention with the bio-membrane, where lipids undergo oxidative stress [117,118]. Guaiazulene exhibits protective effects on embryogenesis that are mediated by its anti-inflammatory properties [119].

4.9. Dyspepsia and gastroesophageal reflux disease (GERD)

The most prevalent gastrointestinal disorder is dyspepsia, which occurs in 20–30 % of people [120,121]. A wide variety of upper-abdominal symptoms, including pain or discomfort, are called dyspepsia. Among the organic causes of dyspepsia are peptic ulcer, GERD, esophageal or stomach cancer, biliary or pancreatic tract abnormalities, and food or medicine intolerance [122]. Approximately 75 % of individuals have idiopathic functional dyspepsia (FD) [123]. PPIs and H2 receptor antagonists are thought to be the best GERD medications.

Nevertheless, they have significant drawbacks with regard to long-term use, including the dangers of stomach flora overgrowth and cellular expansion resembling enterochromaffin [124]. So, looking for natural compounds to cure uninvestigated dyspepsia (UD) is necessary. In this context, guaiazulene might be a potential candidate.

Previous studies have demonstrated that guaiazulene and dimethicone considerably reduce gastrointestinal symptoms and enhance GERD patients' quality of life (QoL). Oral gel (Pepsane®), which contains the active ingredients dimethicone (3 g) and guaiazulene (4 mg) and is administered three times daily before meals, provided symptomatic relief for UD patients with no noticeable side effects and excellent levels of patient satisfaction and strong compliance. The mixture has been shown to be safe and well-tolerated [125]. Similar to GA, azulene derivative KT1–32 enhanced gastric mucosal blood flow in sedated male Wistar rats and showed a gastroprotective effect in an *ex vivo* study [126]. The gastroprotective effect of GA-related compounds might be due to the GIT mucosal covering property. Another research has checked the QoL through the comparative effects of Pepsane® with a placebo drug [127]. The Phase III trial involved 233 people with non-erosive reflux disease (NERD) and mild GERD symptoms. These patients were given Pepsane® or a placebo postprandially at random for 28 days. The primary goal of the study, a 50 % reduction in the overall symptom score at day 14, was achieved in 54.1 % of patients taking Pepsane® *vs.* 41.1 % of patients taking a placebo. In 118 dyspeptic patients, including those with GERD, Pepsane® medication reduced the percentage of patients suffering heartburn from 66 % to 14 % after one month. The therapeutic effect of this combination was felt quite quickly in 82.2 % of patients (< 20 min) [128].

4.10. Lipid disorder

Guaiazulene demonstrated anti-hypercholesterolemic, anti-hyperlipidaemic activity in atherosclerosis and atheromatous in animals and humans without causing toxicity or side effects in the tested animals [129]. To draw any conclusion, more studies are required. Future GA research in this area include additional investigations.

4.11. Nipple fissure or pain

The second most frequent reason for early breastfeeding termination is nipple fissures or pain [130]. It is a massive cutaneous abrasion that has developed in the areola and nipple that can cause ulcerations, blisters, fissures, skin damage, edema, erythema, and dark patches [131]. Many factors, including mechanical stresses, physiological reactions, and infections, are commonly responsible for nipple discomfort and fissures. Several treatments for nipple fissures have been proposed, including hydrogels, warm compresses, tea bags, mint sweat, enhanced collagenase ointment, honey, dexpanthenol, breast milk, and lanolin, but they are associated with some skin problems and adverse effects over long-term use [132]. Therefore, it is necessary to look for natural ingredients to alleviate the pain or nipple fissure. In this situation, the GA might potentially relieve pain or nipple fissures.

Herbal medicine has a long history with the greatest therapeutic solution in human civilization [133–135]. This review gives a common source of GA in health care [136] with clinically available information and evidence regarding nipple fissures and the prevention and treatment of pain. According to API et al., [137] GA ointment (0.05 % *w*/w) has been shown to prevent nipple fissures in 153 mothers after using the instrument visual analog scale (VAS) to evaluate pain severity [132, 138].

4.12. Antidiabetic agent

Diabetes mellitus (DM) is a metabolic disorder brought on by prolonged hyperglycemia or insulin resistance. Diabetes is the seventh largest cause of death in the United States (US). It kills approximately 85 thousand Americans each year, according to the Centers for Disease Control and Prevention, Department of Health and Human Services of the US. Diabetes is a major public health issue that affected 463 million people worldwide in 2019. By 2030, this figure will reach 578 million, and by 2045, it will reach 700 million [139,140]. Numerous research organizations worldwide have developed innovative, more efficient, and patient-friendly treatments for DM [73]. GA and related compounds have shown possible antidiabetic potential after structure modification. In one study, a series of C-glucosides with azulene rings in the aglycon moiety was synthesized, and the inhibitory activities toward hSGLT1 and hSGLT2 were evaluated. They found **8e** is a more potent SGLT2 inhibitor, which displayed a strong and long-lasting antihyperglycemic effect on STZ type 1 diabetic rats and KK/Ay type 2 diabetic mice following oral administration. Additionally, *in vitro* inhibition of human sodium-glucose transport protein 1 (hSGLT1) and (hSGLT2) was also assessed using Chinese hamster ovary cells (CHO). Additionally, a mono-choline salt of **8e** (YM543) compound was selected as a clinical candidate [141]. In two separate trials, the researchers determined the IC_{50} values of azulene derivative for hSGLT2 and selectivity for hSGLT [142]. 90 % of glucose reabsorption is mediated by SGLT-2, primarily expressed in the proximal portion of the kidney, and causes DM. By blocking SGLT-2 transport in the kidney. By blocking SGLT-2 transport in the kidney, GA inhibits the development of diabetes mellitus by increasing the excretion of glucose in urine and lowering plasma glucose levels (Fig. 8) [143].

Furthermore, the antihyperglycemic efficacy of GA derivatives was confirmed in pre-clinical investigations on type 2 diabetic KK/Ay mice. In this investigation, an azulene derivative (3 mg/kg) successfully reduced blood glucose levels in the vehicle by 46 %. After then, the azulene derivative was further improved, leading to the development of a new molecule. This new molecule was later found to be the most prevalent auspicious substance in the sequence. It was projected for use in clinical studies as mono choline salt, also known as mono choline salt YM543 [144].

4.13. Cardiovascular diseases

Worldwide, cardiovascular diseases (CVDs) constitute the leading cause of death [145]. 1.7 billion people (22 % of the world's population), it is estimated, have at least one underlying condition, such as hypertension, which increases the risk of a major illness in the event of coronavirus infection [146]. GA and other azulene derivatives have shown positive outcomes in cardiovascular diseases [88]. Researchers from the Medical University of Yamanashi in Japan initially created GA and azulene derivatives with the potential to be cardioprotective. They used the clinically effective antianginal drug nicorandil as a model to develop novel GA and other azulene compounds with cardiovascular effects. Nicorandil is a 2-aminoethanol derivative of nicotinic acid with

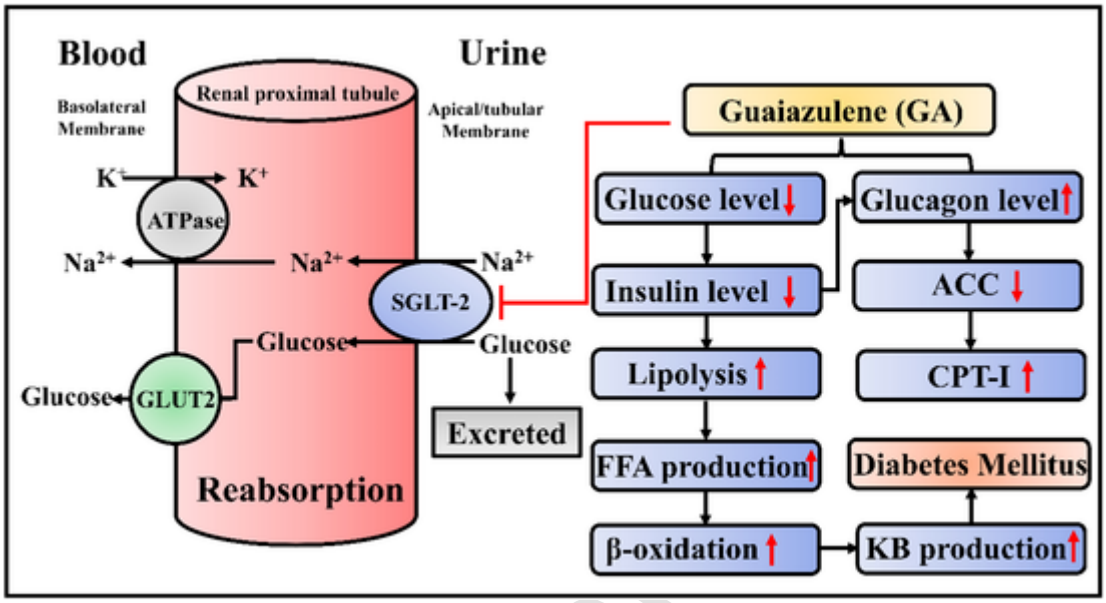

Fig. 8. GA reduces glucose levels *via* inhibiting the SGLT-2 co-transporter in the proximal region of the kidney and other mechanisms to prevent diabetes mellitus. (Abbreviation: ACC; acetyl CoA carboxylase, CPT; Carnitine palmitoyl transferase-1, FFA; Free fatty acids, KB; ketone bodies).

potent cardiovascular properties. In the actual procedure for developing azulene derivatives, the structure of nicorandil was divided into three groups: A, B, and C. Based on this structure, GA, 4,6,8-trimethylazulene, and azulene structures were synthesized [147]. Utilizing the perfused blood from a dog heart, the effects of these newly synthesized azulene derivatives on coronary blood flow were evaluated. The potency ranking was observed in the following order: Guaiazulene > 4,6,8-trimethylazulene > azulene. In isolated rabbit aorta strips, the azulene-1-carboxamidine derivative of HNS-321 exerts strong vascular relaxant effects. According to SAR studies, HNS-32 shows depressor action due to the presence of a pyridine ring. On the other hand, its antiarrhythmic and adverse chronotropic actions strongly correlate with the guaiazulene methyl groups at the 3 and 8 locations [88].

4.14. Neurological disorders

GA and GA-related compounds were evaluated for their affinities to monoaminergic G protein-coupled receptors, including dopaminergic, histaminergic, serotonergic, and adrenergic receptor subtypes. CHO cells were employed to evaluate the receptor binding properties *in vitro*. One of GA's neuroleptic effects was inhibiting the stereotyped behavior brought on by dopaminergic stimulants. FAUC3019 is an azulenylmethylpiperazine compound tested to cure erectile dysfunction. It is a partial agonist for the dopamine D4 receptor [142,148]. FAUC3019 promotes a penile erection by activating the human dopamine D4 receptor and the oxytocinergic pathway in the paraventricular nucleus (PVN) region. L-arginine is converted to NO by oxytocinergic neurons when nNOS is activated by an increase in Ca^{2+} influx, which causes an increase in NO production in the PVN portion. NO causes the oxytocinergic neuronal cells to release oxytocin, which is responsible for penile erection. These neuronal cells are located in the spinal cord and extrahypothalamic regions of the brain (Fig. 9) [73,149]. Following subcutaneous administration and PVN injection, the second *in vivo* research of GA-related compounds was carried out on 32 male rats, and they showed penile erection. Its effectiveness was greater than that of apomorphine, the conventional medication. GA and GA-related compounds demonstrated a high degree of D4 receptor affinity, selectivity, and dipole moment. To compare this study's findings to popular erectile dysfunction medications, such as tadalafil and sildenafil, more research is needed in this area [150].

Turku et al. proposed azulene compounds to synthesize orexin (hypocretin) OX1 and OX2 receptor ligands using an *in-silico* approach [151]. Since these receptors are important in the sleep cycle, orexin antagonists could be used to treat insomnia. These agonists can also help treat narcolepsy and daytime sleepiness. There were found to be seven powerful and two weaker double agonists of the orexin receptor. The activity was assessed by measuring the Ca^{2+} response in the CHO-K1 cell line expressing heterologously high quantities of human OX1 and OX2 receptors. The orexin-A response on the OX1 receptor was boosted by several GA-related compounds, some of which were weak orexin receptor agonists [73].

Despite brand-new synthetic GA-related compounds, plants still contain many more GA-related compounds. Ergosterol ganotheaecolin A, isolated by *Luo* et al. [152] in the fungus *Ganoderma theaecolum*, can potentially treat many neurological conditions [152]. The fungus is frequently used in traditional Chinese medicine to treat neurological diseases [73].

4.15. Antifungal

When tested *in vitro* against the fungus *Aspergillus niger*, *Matricaria chamomilla* L. oil, which contains GA and other chemical components, was found to have strong antifungal properties. Compared to the control at ≥125 g/mL, the plant oil demonstrated a fungistatic effect against the fungus at all concentrations [13]. The antimicrobial inquiry used certain bacteria and fungi. It was fascinating to look at the antifungal properties of azulene-organobismuth (III) carboxylates. With azulene derivatives, Murafuji et al. developed several heterocyclic compounds called organobismuth (III) carboxylates. In a qualitative antifungal assay on *Saccharomyces cerevisiae* W303-1A yeast, they utilized DMSO as a negative control. They discovered that this chemical was extremely lipophilic and demonstrated a strong level of fungal growth inhibition [153].

The effectiveness of GA against group *G streptococci* was demonstrated when its antifungal activity was compared to that of anethole, carvacrol, eugenol, cinnamon bark oil from *Cinnamomum zeylanicum*, and thymol. Carvacrol, on the other hand, was discovered to be the most effective substance in terms of antifungal activity, preventing

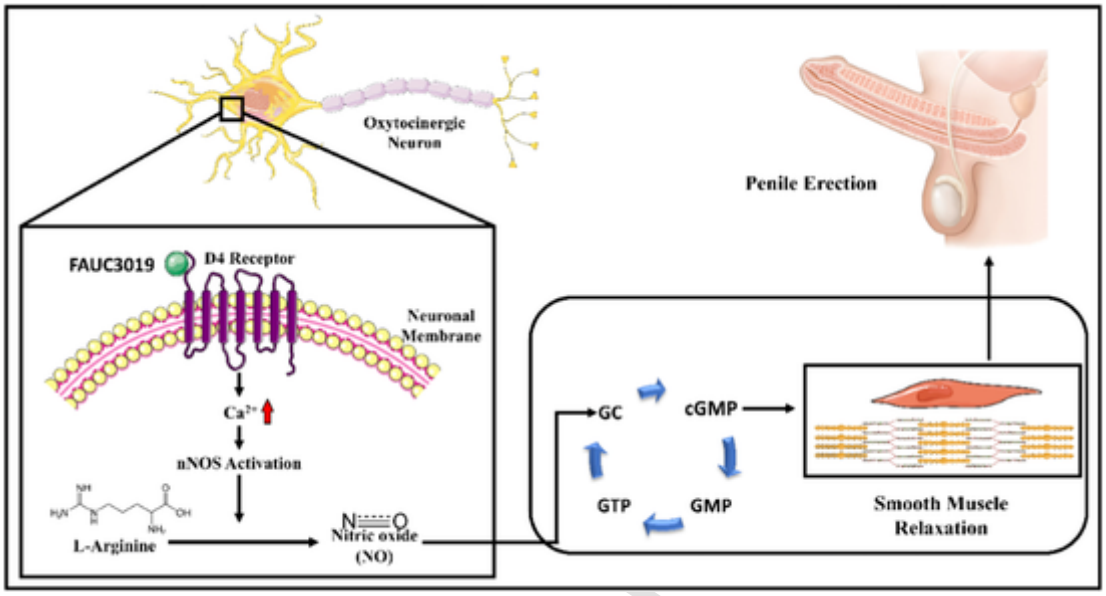

Fig. 9. Mechanism of FAUC3018 in penile erection.

90 % of group *G streptococci* strains from growing at a concentration of 236.7 g ml^{-1} [104]. The lifetime toxicity of GA with *Pleurotus fungus* species was used to test its antifungal efficacy in *Drosophila melanogaster*. Female and male populations of *D. melanogaster* lived shorter lives due to dose-time interaction, and GA showed antifungal efficacy. In a different study, *Pleurotus sajor-caju* (PSCwt) and *Pleurotus osteratus* (POwt), two edible fungi, were mixed with GA to exhibit a healing effect and increased longevity. GA's antifungal activity was confirmed when it reduced *D. melanogaster's* life span [154].

5. Clinical trials on guaiazulene and related compounds

Guaiazulene and its related compounds have been shown to have anti-inflammatory effects in several clinical studies. A cosmetic containing GA (0.02 %) has shown an anti-inflammatory effect in atopic dermatitis patients and relieves itching [155]. In a clinical study on breastfeeding women, GA (0.05 %) ointment preparation has shown an anti-inflammatory effect by preventing sore and cracked nipples [137]. Another study on oral mucositis patients has shown that mucosa-adhesive water-soluble polymer film (AD film) containing GA has anti-inflammatory and antibiotic activity to prevent oral mucositis and other oral infections [68]. GA (4 mg) gel preparation has shown a protective effect against un-investigated dyspepsia patients and improved GERD [125]. Currently, no clinical trials have been reported on clinical.gov.in for guaiazulene and its related compounds. Therefore, GA and its related compound might be novel for clinical trials conducting a study to prevent various inflammatory consequences. On the other hand, these compounds could be novel for clinical study and clinical trials for various diseases, including cancer, hepatitis, neurotoxicity, cardiotoxicity, diabetes, and various types of infection shown in previous *in vitro* and *in vivo* studies.

6. Future perspectives

Guaiazulene (GA), derived from plants like *M. chamomilla* L, has a wide range of functions, including anti-inflammatory, antiseptic, antimicrobial, antioxidant, epithelializing, antimutagenic, immunomodulatory, fungicidal, expectorant, diuretic, diaphoretic, demulcent, and bitter stimulant properties. Numerous *in vitro* and *in vivo* investigations have demonstrated the favourable, helpful effects of GA in a wide range of diseases. As a result, it may be a useful option to treat various illnesses, such as cancer, ulcers, inflammation, microbial infections, diabetes, cardiovascular and neurological ailments. Due to its lipid solubility, it can easily traverse the blood-brain barrier and may therefore be effective in treating neurological illnesses. It is necessary to create GA-based nanoformulations for targeted distribution in neurological, immunological, and cancer cases. However, much more research is needed to confirm GA's potential as a therapeutic candidate. In addition, there is a need to investigate certain illnesses that have not yet been studied. Data suggest that it could be the best alternative for treating nipple fissures or pain and diaper dermatitis.

7. Conclusion

Guaiazulene has gained recognition for its pleiotropic health effects, especially due to its anti-inflammatory and antioxidant properties. Studies have supported the use of GA to manage disorders such as bacterial infections, tumors, immunomodulation, expectorants, diuretics, diaphoresis, ulcers, dermatitis, proliferation, and gastritis, where lipid peroxidation or inflammatory response is a crucial pathological component. Additionally, it aids in the management of drug- and exercise-induced hepatotoxicity, improving recovery and subsequent performance. Moreover, a relative dose of GA with photodynamic therapy using a 635 nm red laser exhibits anti-inflammatory effects in fibroblasts and mononuclear cells from peripheral blood. Clinically, the use of local pomade (0.05 g/100 g) for diaper dermatitis might still be beneficial for those who do not have a diagnosed medical problem. The evidence suggests that GA has beneficial effects on hepatotoxicity, inflammation, bacterial illness, and diaper dermatitis, but more extensive studies are required before a firm conclusion can be drawn. In conclusion, all the data suggest that GA and its derivatives might open a new avenue for treating different pathological conditions. Still, there is a need to find or synthesize a GA-derivative with a more specific pharmacological effect and lower toxicity and subsequently access them for their therapeutic benefits over the GA and already developed GA-related compounds.

Abbreviations

DPPH	2,2-diphenylpicrylhydrazyl
FD	Functional dyspepsia
GA	Guaiazulene

GAS-Na	Sodium guaiazulene sulfonate
GERD	Gastroesophageal reflux disease
GSH	Glutathione
LD_{50}	Lethal dose 50
mTOR	Mammalian target of rapamycin
NAPQI	*N*-acetyl-p-benzoquinone imine
NSCLC	Non–small cell lung cancer
PBMC	Peripheral blood mononuclear cells
PCM	Paracetamol
QoL	Quality of life
UD	Uninvestigated dyspepsia
fMLP	N-Formyl-methionyl-leucyl-phenylalanine
DSB	Double-strand break
PIKK	Phosphatidylinositol 3-kinase-related kinase
TXA2	Thromboxane A2
PGH2	Prostaglandin H2

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The data presented in this study are available in article.

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