Alpinia zerumbet anxiolytic and antidepressant effects: a literature review

ABSTRACT

Studies demonstrated that many elderly individuals suffer from depressive and anxiety disorders. The drugs used to treat these disorders cause adverse effects such as sedation, gastrointestinal discomfort, and locomotor deficits, which are often responsible for treatment abandonment. Literature data also describe that older people may be refractory to pharmacological treatments used to combat depressive and anxiety disorders, which is potentially worrying due to the suicide risk associated with these conditions. Previous research reported the medicinal plant's beneficial potential in psychiatric disease treatment due to its antioxidant, anti-inflammatory, and antiapoptotic actions. This paper reviews the *Alpinia zerumbet* actions, a medicinal plant with antidepressant and anxiolytic effects, through increases in noradrenergic neurotransmission and decreases oxidative stress on the central nervous system by increasing antioxidant activity. Moreover, *Alpinia zerumbet* also causes a reduction in IL-6 and elevates BDNF levels in the hippocampus, contributing to its antidepressant, anxiolytic, and anti-inflammatory actions. The adverse effects reduction, combined with the fact that there is no toxicity when ingested by humans and increased longevity, suggests that this medicinal plant is promising for older individuals treatment who suffer from depression and anxiety.

Keywords: Alpinia zerumbet, polyphenols, depression, anxiety, elderly individuals

1. INTRODUCTION

In old age, depression is one of the causes of mental illness, affecting mainly individuals with health problems, who have a cognitive impairment, or living in residential care. Moreover, anxiety disorder is more common than depression in these individuals. The most prevalent types of disorders are generalized anxiety and specific phobias [1]. Ageism is also associated with deterioration in mental health. The World Health Organization (WHO) revealed this relationship by analyzing 422 studies from 45 countries. Around 96% of studies that examined the relationship between ageism and mental health found evidence that ageism influenced psychiatric conditions. These data suggested new insights relating aging to the emergence of depression, anxiety, and cognitive deficits, especially in individuals who suffer from the negative age stereotype [2].

Depressive disorder commonly manifests diminishes the life quality in older adults, manifesting through symptoms such as sadness, feelings of guilt or low self-esteem, feelings of tiredness and lack of concentration, loss of interest or pleasure, and sleep or appetite disorders, which can lead to suicidal ideation. The main types of depressive disorders are major depressive disorder or depressive episodes and dysthymia. The first two present the

symptoms mentioned above, which can be mild, moderate, or severe. While in dysthymia, the symptoms are less intense but last longer [3].

Studies have shown that depression affects around 33.5% of the Japanese elderly population, 17.6% in the United Kingdom, and 17.2% in the United States [4–6]. These data are worrying due to the high rate of suicides in individuals suffering from depressive disorder. The WHO recognized suicide as a public health problem. According to a survey carried out in 2014, age is a risk factor for suicide, with the highest rates among people aged 65 and 70 or over and, secondly, between 30 and 49 years old [7].

According to the Brazilian Society of Geriatrics and Gerontology (BSGG), the most frequent cause of suicide is undiagnosed, untreated, or inadequately managed depression. BSGG points out that approximately 70% of suicide cases are related to depression in this stage of life, usually the first one these people go through. In depressed older people, the main risk situations that deserve to be observed and monitored are those related to losses, such as the anniversary of the loss of a husband/wife or wedding anniversary, among other painful situations. Another alarming fact pointed out is that in terms of successful attempts in older people, it is around 100%, while in people of other age groups, it is ten to one. In general, when the older person is not able to carry out the suicidal act, cognitive deficit or some motor incoordination is suspected [8].

Already, the main symptoms of anxiety disorders are feelings of fear and anxiety that are out of focus and out of scale due to the perceived threat. These symptoms can be mild, moderate, or severe and tend to be chronic. The anxiety disorders described are generalized anxiety, panic, specific phobias, social anxiety, post-traumatic stress, and obsessive-compulsive disorders [3].

Literature data demonstrated that anxiety affects approximately 1.2% to 15% of community samples of elderly individuals and 1% to 28% of clinical samples of elderly individuals [1], showing that anxiety in old age is a highly prevalent psychiatric condition and that as life expectancy increases, it will become a widespread problem in old age [9].

Psychiatric disorders treatment in older patients is a clinical challenge, as physical comorbidities and cognitive dysfunction can be difficult in both diagnosis and use of medicines [10]. Some studies have shown that patients often do not continue using antidepressant and anxiolytic drugs due to the delay in the onset of therapeutic effects and improvement in mood and because of the adverse effects of these medications. The main adverse effects of these two classes of drugs are headaches, sexual dysfunction, seizures, dependence, and suicidal ideation [11,12]. Notably, the use of medicinal plants to treat depression and anxiety promotes beneficial effects on these psychiatric illnesses and drastically reduces the occurrence of adverse effects [13–15].

Pharmacology's challenge is to offer a promising, consistent, low-toxicity, and low-cost therapy for patients. In this context, medicinal plants have achieved a prominent role. Among the various substances extracted from plants, polyphenols have demonstrated great therapeutic potential. The benefits of these compounds may be related to their antioxidant, anti-inflammatory, and anti-apoptotic action [16,17]. *Alpinia zerumbet* (*Zingiberaceae* family) is a medicinal plant rich in polyphenols, native to East Asia and widespread in Brazil's northeast and southeast regions. This medicinal plant has a characteristic aroma that makes it popularly known as cologne. In this context, the traditional use of *Alpinia zerumbet* leaves is due to its antihypertensive, diuretic, and antiulcerogenic effects [18]. Previous studies have demonstrated the beneficial potential of this medicinal plant in cardiovascular and metabolic

changes [19–21]. Besides these peripheral effects, data from the literature also showed its actions in depressive and anxiety disorders [22–24].

Given the high prevalence of depression and anxiety in older people and the increased risk of suicide associated with psychiatric illnesses in this population, this paper aims to carry out a review of the antidepressant and anxiolytic effects of *Alpinia zerumbet* a medicinal plant, which causes beneficial effects cardiovascular and metabolic disorders, which could provide a new perspective for the treatment of these psychiatric diseases in elderly individuals.

2. PATHOPHYSIOLOGY OF DEPRESSION AND ANXIETY

Major depressive disorder is one of the causes of disability that profoundly affects the lives of individuals affected by the disease and their families [25]. Studies have shown that several factors may be related to the pathophysiology of depression, such as changes in the noradrenergic, serotonergic, dopaminergic, and glutamatergic systems. Moreover, oxidative stress, neuroinflammation, hyperactivation of the hypothalamic-pituitary-adrenal axis (HPA), imbalance of neurodegeneration, and neuroprotection-related factors are also associated with this disorder's development [26,27].

The monoaminergic hypothesis of depression explains that a deficit of monoamines, such as dopamine, serotonin, and norepinephrine, may be responsible for the symptoms of this disorder [28]. The mechanism involved in the major of neurotransmission interruption is neurotransmitter reuptake. Therefore, reuptake inhibition can increase neurotransmission, prolonging the neurotransmitter's residence time in the synapse. Most drugs used in clinical practice inhibit the serotonin transporter (SERT), the noradrenaline transporter (NET), or both [26]. The long-term effects of antidepressant drugs evoke adaptive or regulatory mechanisms that increase the effectiveness of therapy. These responses include increased adrenergic or serotonergic receptor density or sensitivity, increased receptor-G protein coupling and activation of intracellular second messengers, induction of neurotrophic factors, and neurogenesis [29]. Evidence suggests that antidepressants increase the expression of brain-derived neurotrophic factor (BDNF), a neurotrophin involved in neuronal plasticity, which appears to be related to these drugs' final mechanism of action [30]. Besides, a recent study demonstrated reduced BDNF levels in the hippocampus and prefrontal cortex of depressive patients [31].

In situations of chronic stress, such as depression and anxiety, hyperactivation of the HPA occurs. This axis activation promotes the release of corticotropin-releasing hormone by neurons in the hypothalamic paraventricular nucleus, which stimulates the anterior pituitary gland to release adrenocorticotropic hormone into the circulation. Finally, this hormone stimulates the adrenal cortex to release corticosteroids, cortisol in humans, and corticosterone in rats. Excess circulating corticosteroids reduce the serotonin 5-HT1A receptors sensitivity, impairing the hippocampus' resilience and ability to deal with stress [32]. Moreover, the HPA axis hyperactivity impaired the BDNF actions, demonstrating the intimate relationship between this neurotrophin and chronic stress induced by depressive and anxiety disorders [33]. A previous study showed that hyperactivity of the HPA axis is a predictor of suicide in elderly mood disorders inpatients [34]. Besides, escitalopram, a selective serotonin reuptake inhibitor, reduces HPA axis hyperactivation in older people with generalized anxiety disorder [35].

Excitotoxicity is also related to oxidative stress and mood disorders. Glutamate is the excitatory neurotransmitter, but its excess causes an increase in intracellular calcium concentrations through the activation of its NMDA receptors, activating enzymes responsible for the generation of reactive species, such as xanthine oxidase, phospholipase A2, and nitric oxide synthase. Thus, oxidative stress occurs, leading to cellular component degradation,

such as peroxidation of membrane lipids, oxidation of proteins, and DNA damage [36]. A recent study demonstrated that the administration of ketamine, an NMDA receptor antagonist, leads to improvement in depressive conditions, especially in patients resistant to conventional treatment [37]. Data also showed that diets rich in monosodium glutamate led to depressive-like behavior in rodents, such as behavioral despair, anhedonia, and reduced social interaction [38].

Oxidative stress in the central nervous system, in regions such as the brain stem, contributes to the hyperstimulation of the sympathetic nervous system, which occurs in the chronic stress present in anxiety and depression disorders [39,40]. A recent study demonstrated that depressed elderly patients have oxidative stress and anxiety [41]. Furthermore, evidence suggests that antidepressants have antioxidant activity, reducing the generation of reactive species and oxidative stress [42].

Neuroinflammation and oxidative stress are also closely related. Oxidative stress can cause the activation of the NFkB transcription factor, promoting an increase in the synthesis of pro-inflammatory cytokines. Notably, studies have reported the association between inflammation and depressive disorder development. C-reactive protein and interleukin-6 are inflammatory markers very present in depression and linked to symptoms such as anhedonia [43]. In agreement with these data, recent discoveries have demonstrated that anti-inflammatory substances can have antidepressant effects [44]. Besides, the pro-inflammatory factors release and microglial activation are related to anxious and depressive-like behavior [45–48]. Aging impairs the peripheral immunological communication with the central nervous system, promoting a pro-inflammatory state and causing an increase in peripheral immune responses. The prolongation and exacerbation of these immune responses can develop changes in the circuits involved with emotions and cognition relevant to geriatric depression [49].

Medicinal plants have demonstrated their potential in the treatment and prevention of psychiatric illnesses, such as depression and anxiety. In a recent study, my research group demonstrated the beneficial effects of polyphenols from medicinal plants in the treatment of anxiety-type disorders. These phenolic compounds caused a reduction in the hyperactivity of the HPA axis, activation of the NO-BDNF-TRKB pathway in the central nervous system, and an antioxidant effect that contributes to the improvement of neuroplasticity, oxidative stress and monoaminergic systems involved in the genesis of anxious behavior [17]. These findings highlight medicinal plant potential in the treatment of anxiety and depression disorders.

3. *Alpinia zerumbet*

3.1. CHEMICAL COMPOSITION

The use of medicinal plants and their derivatives has gained more and more followers as individuals have sought a healthier lifestyle. Therefore, there has been an increase in the consumption of supplements derived from plants and phytotherapeutics for various disease treatments, including psychiatric ones [12].

Alpinia zerumbet is a medicinal plant rich in polyphenols, native to East Asia. However, it has adapted well to the climatic conditions of Brazil, where it has become widely spread in the northeast and southeast regions. This medicinal plant is popularly known as cologne due to its characteristic odor. Moreover, the population uses its leaves in traditional medicine for their antihypertensive, diuretic, and antiulcerogenic actions [18,50].

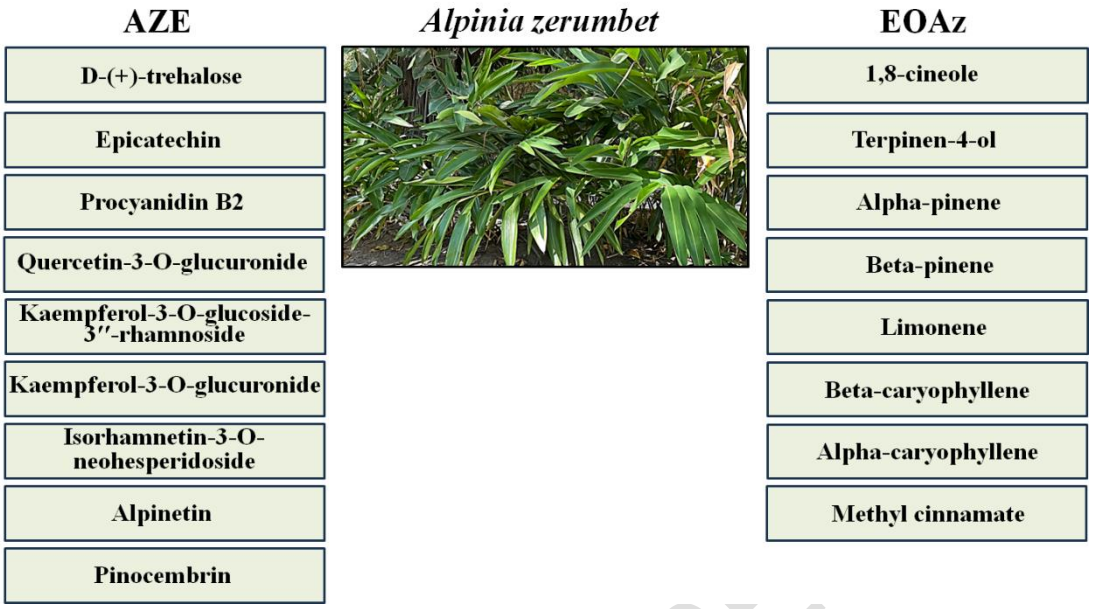

Fig. 1. *Alpinia zerumbet* illustrative diagram demonstrating the chemical compounds present in the hydroalcoholic fresh leaf extract of the plant and extracted from the essential oil. AZE - *Alpinia zerumbet* hydroalcoholic fresh leaf extract, EOAz - *Alpinia zerumbet* essential oil.

The leaves of *Alpinia zerumbet* contain polyphenols such as procyanidins, catechins, epicatechins, kaempferol-3-O-glucoside, and rutin, and also include kavalactones such as 5,6-dehydrocavaine and Kavain [18,51]. These chemical compounds promoted the biological effects of this medicinal plant, including LDL cholesterol oxidation-reduction, anti-inflammatory effects, and improved atherosclerosis [52–54]. In addition to the previously mentioned actions, literature data also showed that *Alpinia zerumbet* promotes anti-obesity, hypoglycemic, and anti-cancer effects [19,54].

A recent study by our group investigated the chemical composition of different preparations of *Alpinia zerumbet* extract, demonstrating that the hydroalcoholic extract prepared from fresh leaves subjected to boiling has a more expressive polyphenolic content than the aqueous extract of the fresh leaf and then the aqueous and hydroalcoholic extracts prepared with the dried leaves. This data also reinforced the greater potency of the hydroalcoholic extract of the fresh leaf in producing a vasodilatory effect in the mesenteric arterial bed, an in vitro evaluation, compared to the other extracts analyzed [55]. *Alpinia zerumbet* hydroalcoholic extract of the fresh leaf (AZE) chemical composition analyses demonstrated that this extract is composed of trehalose, epicatechins, procyanidin B2, quercetin-3-O-glucuronide, kaempferol-3-O glycoside, kaempferol-3-Glucoside-3”-rhamnoside, pinocembrin and alpinetin. Furthermore, compared to other extracts, AZE has high concentrations of epicatechins (33%), procyanidin B2, and pinocembrin (Fig. 1) [55]. Moreover, our group demonstrated the antihypertensive and antioxidant action of the *Alpinia zerumbet* hydroalcoholic extract prepared from fresh leaves in a model of spontaneous hypertension, data submitted for publication.

Another research group analyzed the chemical composition of the essential oil obtained from the leaves of *Alpinia zerumbet*, showing that it is composed of the p-Cymene, the most abundant compound, followed by 1,8-cineole, terpinene-4-ol, alpha-pinene, beta-pinene and

limonene. It also has beta-caryophyllene, alpha-caryophyllene, and finally methyl cinnamate (Fig. 1) [22]. These data highlight composition differences between essential oil and leaf extracts from *Alpinia zerumbet*.

Despite the previously reported cardiovascular and metabolic effects of *Alpinia zerumbet*, this medicinal plant also promotes beneficial effects on the central nervous system, enabling its use for depressive and anxiety disorders treatment, as will be discussed later.

3.2. *Alpinia zerumbet* IN DEPRESSIVE DISORDER

The high number of elderly individuals affected by depressive disorder and anxiety tends to increase even more, considering that the life expectancy of the world population is increasing, which requires treatments that reduce symptoms and cause minimal adverse effects since they continue to be underdiagnosed and undertreated, causing suffering and social burdens. As previously demonstrated in the introduction, depressive and anxiety disorders profoundly affect elderly individuals, who often abandon pharmacological treatment due to adverse effects, making them vulnerable to suicide. The medicinal plants used preventively or as treatment can offer an alternative to conventional pharmacological therapy, promoting beneficial effects in these diseases' treatment with fewer adverse effects.

Previous studies demonstrated that *Alpinia zerumbet* administration promotes beneficial effects in depressive-like behavior (Fig. 2 and Table 1) [24,56]. Notably, in the animal model, the treatment with the hydroethanolic extract of dried leaves of *Alpinia zerumbet*, when administered orally, using intragastric gavage, an important indicating oral bioavailability, reduced the immobility time in the tail suspension test, as caused by imipramine, a tricyclic antidepressant [56]. Moreover, another research demonstrated the antidepressant effect of *Alpinia zerumbet* in mice treated with a hydroethanolic extract of dried leaves investigated in a tail suspension test, an effect related to the dopaminergic and serotonergic systems [24]. In this study, the authors evaluated the involvement of dopamine, norepinephrine, serotonin, and glutamate in the antidepressant effect of *Alpinia zerumbet*, using inhibitors of the synthesis of these neurotransmitters or antagonists of their actions. The monoamine synthesis inhibitor, D, L-α-Methyl-ρ-tyrosine (AMPT), can cause a high reduction in noradrenaline and dopamine levels without promoting changes in serotonin levels [57]. Mice pre-treatment with this inhibitor prevented the establishment of *Alpinia zerumbet* extract antidepressant effect in the tail suspension test. These findings suggest that the antidepressant action of the extract is dependent on the availability of dopamine and/or noradrenaline in the nerve terminal (Fig. 2 and Table 1) [24].

The role of adrenergic neurotransmission in depressive disorder can be demonstrated through the effect of reserpine, an antihypertensive drug that interferes with the storage and uptake of noradrenaline, causing the therapeutic effect but also the depression symptoms in several patients. Another important finding is the effective action of the norepinephrine reuptake inhibitors in depressive disorder treatment [26]. A previous study highlighted the AMPT effect administration, demonstrating that 11 of the 18 patients subjected to this inhibitor had a return of depressive symptoms and a decrease in cerebral metabolism in several areas of the cerebral cortex, with an elevated effect in the orbitofrontal and dorsolateral prefrontal cortex regions, as well as thalamus [58]. These data prove the importance of adrenergic neurotransmission in the occurrence of depressive disorder and highlight the promising effect of *Alpinia zerumbet* for the treatment of this psychiatric disease since its actions involve the participation of noradrenaline, a pharmacological mechanism with proven efficacy. The study by Bevilaqua and collaborators also evaluated the antagonism of glutamate AMPA receptors, which did not alter the antidepressant effect of the hydroethanolic dried leaves extract of *Alpinia zerumbet*. However, the authors did not exclude the possibility of the participation of

metabotropic or NMDA receptors in this effect, mechanisms that still need to be elucidated [24].

Table 1. Promissing *Alpinia zerumbet* effects on animal models and humans, perspective for depressive and anxiety disorders treatment in older patients.

STUDY	YEAR	*Alpinia zerumbet* EFFECTS	EXTRACT TYPE AND CONCENTRATIONS
Animal models			
Bevilaqua et al.,	2016	Depressive-like behavior in AMPT, PCPA and NQX administration mice model	Hydroethanolic extract from dried leaves using 800 mg/Kg
Roman Junior et al.,	2013	Depressive-like behavior on the tail suspension test in mice	Hydroethanolic extract from dried leaves using 200, 400 and 800 mg/Kg
Bevilaqua et al.,	2016	Act through noradrenergic transmission in AMPT, PCPA and NQX administration mice model	Hydroethanolic extract from dried leaves using 800 mg/Kg
Murakami et al.,	2009	Anxiolytic-like behavior in 5-HTP and fluoxetine administration mice model	Essential oil extract from the leaves using 0.087, 0.87, and 8.7 ppm
Satou et al.,	2010	Anxiolytic-like behavior on the elevated plus-maze test in mice	Essential oil extract from the leaves using 8.7 ppm
Roman Junior et al.,	2013	Anxiolytic-like behavior on on light/dark test in mice	Hydroethanolic extract from dried leaves using 200, 400 and 800 mg/Kg
Murakami et al.,	2009	Increase locomotor activity in 5-HTP and fluoxetine administration mice model	Essential oil extract from the leaves using 0.087, 0.87, and 8.7 ppm
Roman Junior et al.,	2013	Increase antioxidant activity in vitro and in brain	Hydroethanolic extract from dried leaves using 200, 400 and 800 mg/Kg
De Araújo et al.,	2011	Increase antioxidant activity in ketamine mice model	Essential oil extracted from the leaves using 100 and 200 mg/Kg
De Araújo et al.,	2021	Increase antioxidant activity in ketamine mice model	Essential oil extracted from the leaves using 100 and 200 mg/Kg
De Araújo et al.,	2021	Decrease neuroinflammation in ketamine mice model	Essential oil extracted from the leaves using 100 and 200 mg/Kg
De Araújo et al.,	2021	Increase BDNF levels in ketamine mice model	Essential oil extracted from the leaves using 100 and 200 mg/Kg
Humans			
Teschke & Xuan	2018	Increase longevity Not induce toxicity	A pack of dried *Alpinia* powder from leaves, flowers,and rhizome using 2.5 g, dipped in 200–300 mL of hotwater.

AMPT, D, L-α-Methyl-ρ-tyrosine; PCPA, 4-chloro-DL-phenylalanine methyl ester hydrochloride; NBQX, 1,2,3,4-tetrahydro-6-nitro-2,3-dioxo-benzo[f]quinoxaline-7-sulfonamide disodium salt hydrate; 5-HTP, 5-hydroxytryptophan; BDNF, brain-derived neurotrophic factor.

The polyphenols that are part of the composition of the hydroethanolic extract of *Alpinia zerumbet* also play a fundamental role in the antidepressant effect previously described. Phytochemical analyses have shown that this medicinal plant has two flavonoids: rutin and kaempferol-3-O-glucuronide. Previous studies have shown that these polyphenols reduce depressive-like behavior in tail suspension and forced swimming tests [24,59,60].

3.3. *Alpinia zerumbet* IN ANXIETY DISORDER

Previous studies have also reported the anxiolytic effect of *Alpinia zerumbet*. The essential oil extracted from the leaves of this medicinal plant showed reduced anxiety-like behavior in the elevated plus-maze test [22]. Another research demonstrated that *Alpinia zerumbet* essential oil extracted from the leaves inhalation also caused an anxiolytic effect on the elevated plus-maze test [23]. Moreover, previous data also proved that the hydroethanolic extract of dried leaves of *Alpinia zerumbet* has anxiolytic action on light/dark tests (Fig. 2 and Table 1) [56].

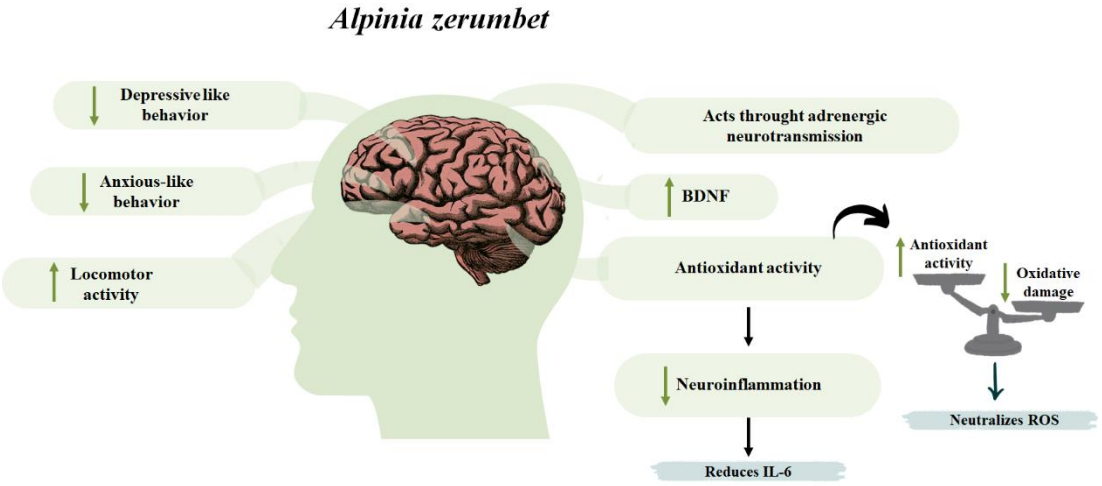

Fig. 2. Scheme summarizing the beneficial effects of *Alpinia zerumbet* that make it a promising medicinal plant for the treatment of depressive and anxiety disorders in elderly individuals. BDNF - brain-derived neurotrophic factor, Il-6 - interleukine-6, and ROS - reactive oxygen species.

Benzodiazepines are a class of drugs used to treat anxiety disorders. In experimental models, these drugs increase the time spent in the open arms of the elevated plus-maze and reduce locomotor activity [61]. Oppositely, the essential oil extracted from the leaves of *Alpinia zerumbet* promotes an increase in locomotor activity and simultaneously increases the time spent in the open arms of the elevated plus maze (Fig. 2 and Table 1) [22]. This effect of *Alpinia zerumbet* is promising for the treatment of older individuals with anxiety disorders, as benzodiazepines can cause cognitive and locomotor deficits, which already occur in the older due to age, and this medicinal plant has a notable anxiolytic action without promoting locomotor changes, demonstrating a more promising action compared to this class of drugs. Finally, the phenolic compounds that are part of the composition of *Alpinia zerumbet* are also

essential for its anxiolytic effect. The essential oil and extracts formulated from this medicinal plant contain limonene and linalool, polyphenols with previously demonstrated potent anxiolytic action [62,63].

3.4. ANTIOXIDANT, ANTI-INFLAMMATORY, AND NEUROTROPHIC *Alpinia zerumbet* ACTIONS CONTRIBUTE TO ANTIDEPRESSANT AND ANXIOLYTIC TREATMENT

As previously highlighted, oxidative stress plays a fundamental role in the pathophysiology of depressive and anxiety disorders. Moreover, it is closely related to neuroinflammation. *Alpinia zerumbet* has a notable antioxidant action, promoting oxidative damage reduction and antioxidant activity elevation (Fig. 2 and Fig.3). Furthermore, the polyphenols present in this medicinal plant have the potential to donate electrons and neutralize reactive species, making them less harmful (Table 1) [56,64,65]. A previous study evaluated the in vitro antioxidant activity of hydroethanolic extract of dried leaves of *Alpinia zerumbet*, demonstrating significant ferric-reduction power, 1,1-diphenyl-2-picrylhydrazyl radical, hydrogen peroxide scavenging activity, and protection against brain lipid peroxidation [56]. Moreover, other data showed that the essential oil extracted from leaves of *Alpinia zerumbet* reduces lipid peroxidation, increases reduced glutathione levels, and also prevents the decrease in nitrite content caused by oxidative stress in the whole brain without the cerebellum in ketamine model [64]. Finally, the essential oil extracted from the leaves of *Alpinia zerumbet* also reverses the hippocampal increased nitrite levels and the endogenous reduced glutathione levels depletion caused by the ketamine model [65].

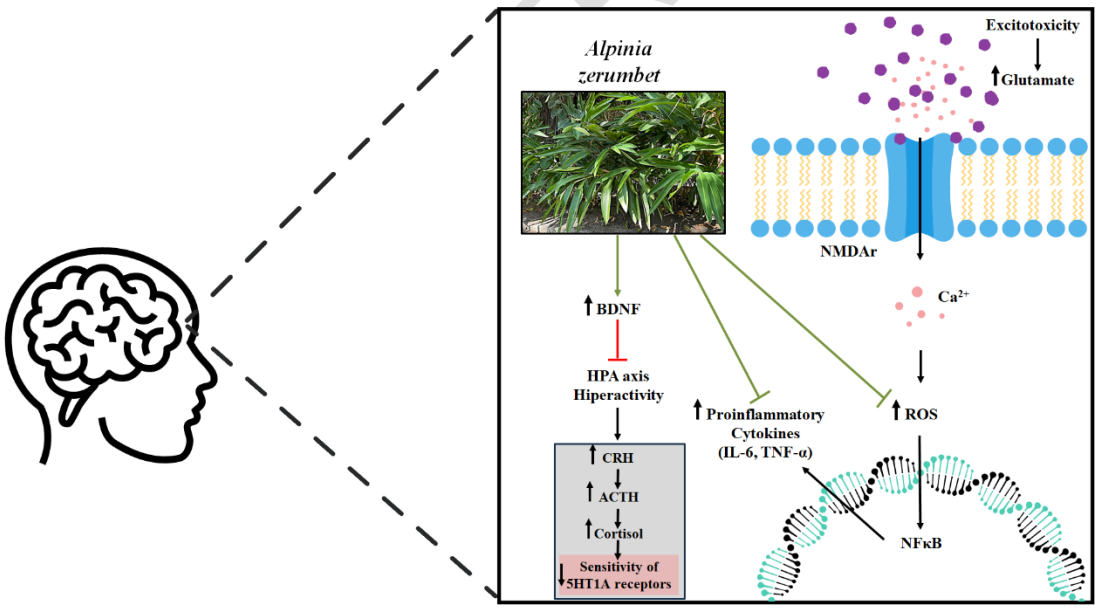

Fig. 3. Scheme summarizing the beneficial effects of *Alpinia zerumbet* that make it a promising medicinal plant for the treatment of depressive and anxiety disorders in elderly individuals. BDNF - brain-derived neurotrophic factor, Il-6 - interleukine-6, and ROS - reactive oxygen species.

This antioxidant actions may contribute to the neuroinflammation decreasing since reactive species can cause the activation of NFkB, increasing the transcription of pro-inflammatory

genes and contributing to the increase in pro-inflammatory cytokines (Fig. 3). This action is potentially relevant since neuroinflammation has an essential role in depression and suicidal behavior [66], elevated in elderly individuals. Notably, a previous study demonstrated that essential oil extracted from the leaves of the *Alpinia zerumbet* reduced IL-6 levels in the hippocampus of rats subjected to ketamine, a model of schizophrenia, highlighting the central anti-inflammatory effect of this medicinal plant (Table 1) [65]. In psychiatric diseases, IL-6 is the most altered pro-inflammatory cytokine [67]. The mechanisms involved in this effect have not yet been elucidated. However, as previously described, the essential oil of *Alpinia zerumbet* is rich in polyphenols, such as the p-Cymene, the most abundant compound, followed by 1,8-cineole, terpinene-4-ol, alpha-pinene, beta-pinene, and limonene. It also has beta-caryophyllene, alpha-caryophyllene, and, finally, methyl cinnamate [22], which contributes to oxidative stress reduction, an essential factor for the transcription of pro-inflammatory cytokines. Thus, the phenolic compounds of *Alpinia zerumbet* reduce neuroinflammation and have antioxidant properties, acting beneficially in psychiatric disorders such as anxiety and depression (Fig. 2 and Fig. 3).

Considering the essential role of BDNF and its fundamental actions in improving depressive and anxiolytic disorders, as demonstrated previously, we highlight that a previous study reported that essential oil extracted from the leaves of the *Alpinia zerumbet* increases the levels of this neurotrophin in the hippocampus of rats subjected to ketamine, a model of schizophrenia (Table 1) [65]. A previous study elucidated that immune response dysregulation and oxidative stress compromise synaptic plasticity, which leads to BDNF reduction [68], as well as the hyperactivation of the HPA axis present in anxiety and depression [32,33]. The *Alpinia zerumbet* bioactive compounds, 1,8-cineole, terpinene-4-ol, and caryophyllene, possess neuroprotective and neuroactive actions, which can contribute to BDNF elevation [69]. This effect also decreased HPA axis hyperactivation, an essential role in the antidepressant and anxiolytic properties of *Alpinia zerumbet*. Further studies are needed to understand the bioactive compound mechanisms in increasing BDNF levels in the central nervous system. Notably, the increase in BDNF demonstrates the promising potential of this medicinal plant for elderly people treatment with psychiatric disorders (Fig. 2 and Fig. 3).

A study carried out in the last decade also suggests the beneficial effects of *Alpinia zerumbet* on humans, reporting that this medicinal plant appears to significantly increase the longevity of the population in Okinawa, Japan (Table 1) [54]. The people of Okinawa consume *Alpinia zerumbet* daily in teas and other beverages containing powdered leaves, flowers, and rhizomes. They also consume its fresh leaves for wrapping Mochi, a traditional rice cake, as vegetable and spice [70]. Besides, on special occasions, *Alpinia zerumbet* leaves are ingested with a steamed bun, fried meat or fish, and in the ice cream to provide a fragrance [54]. The bioactive compounds of *Alpinia zerumbet* have many beneficial effects, such as anti-obesity, anti-lipocytes [71], anti-pancreatic lipase [72,73], anti-dyslipidemia [74], anti-atherosclerosis (including anti-low-density lipoprotein (LDL) oxidation, anti-15-lipoxygenase, anti-tyrosinase) [73,75], anti-diabetes [73], anti-hypertension [76,77], and anti-tumor activities [78,79]. These beneficial properties contribute to increased longevity in the Okinawa population, decreasing the development of cardiovascular diseases, obesity, and tumors, which reduce life expectancy. A study in animal models also demonstrated that *Alpinia zerumbet* elevated the lifespan of *Caenorhabditis elegans* by 22.6% [80], according to data from the Okinawa population [54]. The authors suggested that free radical scavenging effects and its upregulation of stress-resistant gene proteins, including superoxide dismutase-3 (SOD-3) and the heat-shock protein (HSP-16.2), are involved in this *Alpinia zerumbet* effect [80]. However, more research is necessary to elucidate the longevity induced by this medicinal plant. Data from the literature allow us to suggest that *Alpinia zerumbet* acts by inhibiting the reuptake of noradrenaline to promote its antidepressant and anxiolytic effects. However, unlike drugs that act through this mechanism of action, this medicinal plant is safer, as it does not cause

anticholinergic effects and sedation [24]. Studies that demonstrate the properties of the traditional use of *Alpinia zerumbet* and in experimental data do not describe these or other serious adverse effects, which allows us to confirm this safety.

4. CONCLUSION

Depression and anxiety have affected a large number of elderly individuals who are often refractory to available treatments or give up treatment due to adverse effects, increasing their suffering and the risk of suicide. Therefore, *Alpinia zerumbet*, as a medicinal plant with proven anxiolytic and antidepressant action due to its actions of increasing noradrenergic transmission, antioxidant activity and BDNF levels, and decreasing neuroinflammation, could be promising for the elderly individual's treatment. The adverse effects reduction, combined with the fact that there is no toxicity when ingested by humans and increased longevity, suggests that this medicinal plant is promising for older individuals treatment who suffer from depression and anxiety. However, other studies need to deepen our knowledge about its mechanisms in psychiatric diseases.

Disclaimer (Artificial intelligence)
Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during the writing or editing of this manuscript.

REFERENCES

[1] Wolitzky-Taylor KB, Castriotta N, Lenze EJ, Stanley MA, Craske MG. Anxiety disorders in older adults: a comprehensive review. Depress Anxiety 2010;27:190–211. https://doi.org/10.1002/da.20653.

[2] World Health Organization. Global report on ageism 2021.

[3] World Health Organization. Depression and Other Common Mental Disorders 2017.

[4] Wada T, Ishine M, Sakagami T, Okumiya K, Fujisawa M, Murakami S, et al. Depression in Japanese community-dwelling elderly—prevalence and association with ADL and QOL. Archives of Gerontology and Geriatrics 2004;39:15–23. https://doi.org/10.1016/j.archger.2003.12.003.

[5] Zivin K, Llewellyn DJ, Lang IA, Vijan S, Kabeto MU, Miller EM, et al. Depression Among Older Adults in the United States and England. The American Journal of Geriatric Psychiatry 2010;18:1036–44. https://doi.org/10.1097/JGP.0b013e3181dba6d2.

[6] Berntson J, Patel JS, Stewart JC. Number of recent stressful life events and incident cardiovascular disease: Moderation by lifetime depressive disorder. Journal of Psychosomatic Research 2017;99:149–54. https://doi.org/10.1016/j.jpsychores.2017.06.008.

[7] World Health Organization. Preventing suicide: A global imperative 2014.

[8] Brazilian Society of Geriatrics and Gerontology. Depression among the elderly: we need to talk about it 2016.

[9] Balsamo M, Cataldi F, Carlucci L, Fairfield B. Assessment of anxiety in older adults: a review of self-report measures. CIA 2018;Volume 13:573–93. https://doi.org/10.2147/CIA.S114100.

[10] Kok RM, Reynolds CF. Management of Depression in Older Adults: A Review. JAMA 2017;317:2114. https://doi.org/10.1001/jama.2017.5706.

[11] Yeung KS, Hernandez M, Mao JJ, Haviland I, Gubili J. Herbal medicine for depression and anxiety: A systematic review with assessment of potential psycho-oncologic relevance. Phytotherapy Research 2018;32:865–91. https://doi.org/10.1002/ptr.6033.

[12] Kenda M, Kočevar Glavač N, Nagy M, Sollner Dolenc M. Medicinal Plants Used for Anxiety, Depression, or Stress Treatment: An Update. Molecules 2022;27:6021. https://doi.org/10.3390/molecules27186021.

[13] Fajemiroye JO, Da Silva DM, De Oliveira DR, Costa EA. Treatment of anxiety and depression: medicinal plants in retrospect. Fundamemntal Clinical Pharma 2016;30:198–215. https://doi.org/10.1111/fcp.12186.

[14] Sartori SB, Singewald N. Novel pharmacological targets in drug development for the treatment of anxiety and anxiety-related disorders. Pharmacology & Therapeutics 2019;204:107402. https://doi.org/10.1016/j.pharmthera.2019.107402.

[15] Nawrot J, Gornowicz-Porowska J, Budzianowski J, Nowak G, Schroeder G, Kurczewska J. Medicinal Herbs in the Relief of Neurological, Cardiovascular, and Respiratory Symptoms after COVID-19 Infection A Literature Review. Cells 2022;11:1897. https://doi.org/10.3390/cells11121897.

[16] Oppedisano F, Maiuolo J, Gliozzi M, Musolino V, Carresi C, Nucera S, et al. The Potential for Natural Antioxidant Supplementation in the Early Stages of Neurodegenerative Disorders. IJMS 2020;21:2618. https://doi.org/10.3390/ijms21072618.

[17] De Bem GF, Okinga A, Ognibene DT, Da Costa CA, Santos IB, Soares RA, et al. Anxiolytic and antioxidant effects of Euterpe oleracea Mart. (açaí) seed extract in adult rat offspring submitted to periodic maternal separation. Appl Physiol Nutr Metab 2020;45:1277–86. https://doi.org/10.1139/apnm-2020-0099.

[18] Mpalantinos MA, Soares De Moura R, Parente JP, Kuster RM. Biologically active flavonoids and kava pyrones from the aqueous extract of *Alpinia zerumbet*. Phytother Res 1998;12:442–4. https://doi.org/10.1002/(SICI)1099-1573(199809)12:6<442::AID-PTR320>3.0.CO;2-Y.

[19] Chuang C-M, Wang H-E, Peng C-C, Chen KC, Peng RY. Hypolipidemic effects of different angiocarp parts of *Alpinia zerumbet*. Pharmaceutical Biology 2011;49:1257–64. https://doi.org/10.3109/13880209.2011.589856.

[20] Rocha DG, Holanda TM, Braz HLB, De Moraes JAS, Marinho AD, Maia PHF, et al. Vasorelaxant effect of *Alpinia zerumbet's* essential oil on rat resistance artery involves blocking of calcium mobilization. Fitoterapia 2023;169:105623. https://doi.org/10.1016/j.fitote.2023.105623.

[21] Wang S, Xiang J, Zhang G, Fu L, Xu Y, Chen Y, et al. Essential oil from Fructus *Alpinia zerumbet* ameliorates atherosclerosis by activating PPARγ-LXRα-ABCA1/G1 signaling pathway. Phytomedicine 2024;123:155227. https://doi.org/10.1016/j.phymed.2023.155227.

[22] Murakami S, Matsuura M, Satou T, Hayashi S, Koike K. Effects of the essential oil from leaves of *Alpinia zerumbet* on behavioral alterations in mice. Nat Prod Commun 2009;4:129–32.

[23] Satou T, Murakami S, Matsuura M, Hayashi S, Koike K. Anxiolytic effect and tissue distribution of inhaled *Alpinia zerumbet* essential oil in mice. Nat Prod Commun 2010;5:143–6.

[24] Bevilaqua F, Mocelin R, Grimm C, Da Silva Junior NS, Buzetto TLB, Conterato GMM, et al. Involvement of the catecholaminergic system on the antidepressant-like effects of *Alpinia zerumbet* in mice. Pharmaceutical Biology 2016;54:151–6. https://doi.org/10.3109/13880209.2015.1025287.

[25] Pizzagalli DA, Roberts AC. Prefrontal cortex and depression. Neuropsychopharmacol 2022;47:225–46. https://doi.org/10.1038/s41386-021-01101-7.

[26] Dean J, Keshavan M. The neurobiology of depression: An integrated view. Asian Journal of Psychiatry 2017;27:101–11. https://doi.org/10.1016/j.ajp.2017.01.025.

[27] Bhatt S, Nagappa AN, Patil CR. Role of oxidative stress in depression. Drug Discovery Today 2020;25:1270–6. https://doi.org/10.1016/j.drudis.2020.05.001.

[28] Massart R, Mongeau R, Lanfumey L. Beyond the monoaminergic hypothesis: neuroplasticity and epigenetic changes in a transgenic mouse model of depression. Phil Trans R Soc B 2012;367:2485–94. https://doi.org/10.1098/rstb.2012.0212.

[29] Schmidt HD, Duman RS. The role of neurotrophic factors in adult hippocampal neurogenesis, antidepressant treatments and animal models of depressive-like behavior. Behavioural Pharmacology 2007;18:391–418. https://doi.org/10.1097/FBP.0b013e3282ee2aa8.

[30] Sen S, Duman R, Sanacora G. Serum Brain-Derived Neurotrophic Factor, Depression, and Antidepressant Medications: Meta-Analyses and Implications. Biological Psychiatry 2008;64:527–32. https://doi.org/10.1016/j.biopsych.2008.05.005.

[31] Rana T, Behl T, Sehgal A, Srivastava P, Bungau S. Unfolding the Role of BDNF as a Biomarker for Treatment of Depression. J Mol Neurosci 2021;71:2008–21. https://doi.org/10.1007/s12031-020-01754-x.

[32] Vilela LHM, Juruena MF. Avaliação do funcionamento do eixo HPA em deprimidos por meio de medidas basais: revisão sistemática da literatura e análise das metodologias utilizadas. J Bras Psiquiatr 2014;63:232–41. https://doi.org/10.1590/0047-2085000000031.

[33] Kumar A, Kumar P, Pareek V, Faiq MA, Narayan RK, Raza K, et al. Neurotrophin mediated HPA axis dysregulation in stress induced genesis of psychiatric disorders: Orchestration by epigenetic modifications. J Chem Neuroanat 2019;102:101688. https://doi.org/10.1016/j.jchemneu.2019.101688.

[34] Jokinen J, Nordström P. HPA axis hyperactivity as suicide predictor in elderly mood disorder inpatients. Psychoneuroendocrinology 2008;33:1387–93. https://doi.org/10.1016/j.psyneuen.2008.07.012.

[35] Lenze EJ, Mantella RC, Shi P, Goate AM, Nowotny P, Butters MA, et al. Elevated Cortisol in Older Adults With Generalized Anxiety Disorder Is Reduced by Treatment: A Placebo-Controlled Evaluation of Escitalopram. The American Journal of Geriatric Psychiatry 2011;19:482–90. https://doi.org/10.1097/JGP.0b013e3181ec806c.

[36] Meldrum BS. Glutamate as a Neurotransmitter in the Brain: Review of Physiology and Pathology. The Journal of Nutrition 2000;130:1007S-1015S. https://doi.org/10.1093/jn/130.4.1007S.

[37] Onaolapo AY, Onaolapo OJ. Glutamate and depression: Reflecting a deepening knowledge of the gut and brain effects of a ubiquitous molecule. WJP 2021;11:297–315. https://doi.org/10.5498/wjp.v11.i7.297.

[38] Quines CB, Rosa SG, Da Rocha JT, Gai BM, Bortolatto CF, Duarte MMMF, et al. Monosodium glutamate, a food additive, induces depressive-like and anxiogenic-like behaviors in young Rats. Life Sciences 2014;107:27–31. https://doi.org/10.1016/j.lfs.2014.04.032.

[39] Hasler G. Pathophysiology of depression: do we have any solid evidence of interest to clinicians? World Psychiatry 2010;9:155–61. https://doi.org/10.1002/j.2051-5545.2010.tb00298.x.

[40] Ferreira DJS, Da Silva Pedroza AA, Braz GRF, Da Silva-Filho RC, Lima TA, Fernandes MP, et al. Mitochondrial bioenergetics and oxidative status disruption in brainstem of weaned rats: Immediate response to maternal protein restriction. Brain Research 2016;1642:553–61. https://doi.org/10.1016/j.brainres.2016.04.049.

[41] Da Silva LA, Tortelli L, Motta J, Menguer L, Mariano S, Tasca G, et al. Effects of aquatic exercise on mental health, functional autonomy and oxidative stress in depressed elderly individuals: A randomized clinical trial. Clinics 2019;74:e322. https://doi.org/10.6061/clinics/2019/e322.

[42] Khanzode SD, Dakhale GN, Khanzode SS, Saoji A, Palasodkar R. Oxidative damage and major depression: the potential antioxidant action of selective serotonin re-uptake inhibitors. Redox Report 2003;8:365–70. https://doi.org/10.1179/135100003225003393.

[43] Haapakoski R, Ebmeier KP, Alenius H, Kivimäki M. Innate and adaptive immunity in the development of depression: An update on current knowledge and technological advances. Progress in Neuro-Psychopharmacology and Biological Psychiatry 2016;66:63–72. https://doi.org/10.1016/j.pnpbp.2015.11.012.

[44] Troubat R, Barone P, Leman S, Desmidt T, Cressant A, Atanasova B, et al. Neuroinflammation and depression: A review. Eur J of Neuroscience 2021;53:151–71. https://doi.org/10.1111/ejn.14720.

[45] Wang X, Qu Y, Zhang Y, Li S, Sun Y, Chen Z, et al. Antifatigue Potential Activity of Sarcodon imbricatus in Acute Excise-Treated and Chronic Fatigue Syndrome in Mice via Regulation of Nrf2-Mediated Oxidative Stress. Oxid Med Cell Longev 2018;2018. https://doi.org/10.1155/2018/9140896.

[46] Nie X, Kitaoka S, Tanaka K, Segi-Nishida E, Imoto Y, Ogawa A, et al. The Innate Immune Receptors TLR2/4 Mediate Repeated Social Defeat Stress-Induced Social Avoidance through Prefrontal Microglial Activation. Neuron 2018;99:464-479.e7. https://doi.org/10.1016/j.neuron.2018.06.035.

[47] Munshi S, Loh MK, Ferrara N, DeJoseph MR, Ritger A, Padival M, et al. Repeated stress induces a pro-inflammatory state, increases amygdala neuronal and microglial activation, and causes anxiety in adult male rats. Brain, Behavior, and Immunity 2020;84:180–99. https://doi.org/10.1016/j.bbi.2019.11.023.

[48] Yan T, Wang G, Wang L, Liu T, Li T, Wang L, et al. Episodic memory in aspects of brain information transfer by resting-state network topology. Cerebral Cortex 2022;32:4969–85. https://doi.org/10.1093/cercor/bhab526.

[49] Alexopoulos GS, Morimoto SS. The inflammation hypothesis in geriatric depression. Int J Geriat Psychiatry 2011;26:1109–18. https://doi.org/10.1002/gps.2672.

[50] Cartaxo SL, De Almeida Souza MM, De Albuquerque UP. Medicinal plants with bioprospecting potential used in semi-arid northeastern Brazil. Journal of Ethnopharmacology 2010;131:326–42. https://doi.org/10.1016/j.jep.2010.07.003.

[51] Morimoto H, Hatanaka T, Narusaka M, Narusaka Y. Molecular investigation of proanthocyanidin from *Alpinia zerumbet* against the influenza A virus. Fitoterapia 2022;158:105141. https://doi.org/10.1016/j.fitote.2022.105141.

[52] Wattel A, Kamel S, Mentaverri R, Lorget F, Prouillet C, Petit J-P, et al. Potent inhibitory effect of naturally occurring flavonoids quercetin and kaempferol on in vitro osteoclastic bone resorption. Biochemical Pharmacology 2003;65:35–42. https://doi.org/10.1016/S0006-2952(02)01445-4.

[53] Lesjak M, Beara I, Simin N, Pintać D, Majkić T, Bekvalac K, et al. Antioxidant and anti-inflammatory activities of quercetin and its derivatives. Journal of Functional Foods 2018;40:68–75. https://doi.org/10.1016/j.jff.2017.10.047.

[54] Teschke R, Xuan T. Viewpoint: A Contributory Role of Shell Ginger (*Alpinia zerumbet*) for Human Longevity in Okinawa, Japan? Nutrients 2018;10:166. https://doi.org/10.3390/nu10020166.

[55] Da Silva MA, De Carvalho LCRM, Victório CP, Ognibene DT, Resende AC, De Souza MAV. Chemical composition and vasodilator activity of different *Alpinia zerumbet* leaf extracts, a potential source of bioactive flavonoids. Med Chem Res 2021. https://doi.org/10.1007/s00044-021-02791-w.

[56] Roman Junior WA, Piato AL, Marafiga Conterato GM, Wildner SM, Marcon M, Moreira S, et al. Psychopharmacological and antioxidant effects of hydroethanolic extract of *Alpinia zerumbet* leaves in mice. Pharmacognosy Journal 2013;5:113–8. https://doi.org/10.1016/j.phcgj.2013.05.003.

[57] Mayorga AJ, Dalvi A, Page ME, Zimov-Levinson S, Hen R, Lucki I. Antidepressant-like behavioral effects in 5-hydroxytryptamine(1A) and 5-hydroxytryptamine(1B) receptor mutant mice. J Pharmacol Exp Ther 2001;298:1101–7.

[58] Bremner JD, Vythilingam M, Ng CK, Vermetten E, Nazeer A, Oren DA, et al. Regional Brain Metabolic Correlates of α-Methylparatyrosine–Induced Depressive Symptoms: Implications for the Neural Circuitry of Depression. JAMA 2003;289:3125. https://doi.org/10.1001/jama.289.23.3125.

[59] Machado DG, Bettio LEB, Cunha MP, Santos ARS, Pizzolatti MG, Brighente IMC, et al. Antidepressant-like effect of rutin isolated from the ethanolic extract from Schinus molle L. in mice: Evidence for the involvement of the serotonergic and noradrenergic systems. European Journal of Pharmacology 2008;587:163–8. https://doi.org/10.1016/j.ejphar.2008.03.021.

[60] Herrera-Ruiz M, Zamilpa A, González-Cortazar M, Reyes-Chilpa R, León E, García MP, et al. Antidepressant effect and pharmacological evaluation of standardized extract of flavonoids from Byrsonima crassifolia. Phytomedicine 2011;18:1255–61. https://doi.org/10.1016/j.phymed.2011.06.018.

[61] Yamaguchi T, Togashi H, Matsumoto M, Yoshioka M. Evaluation of anxiety-related behavior in elevated plus-maze test and its applications. Folia Pharmacol Jpn 2005;126:99–105. https://doi.org/10.1254/fpj.126.99.

[62] Fukumoto S, Sawasaki E, Okuyama S, Miyake Y, Yokogoshi H. Flavor components of monoterpenes in citrus essential oils enhance the release of monoamines from rat brain slices. Nutritional Neuroscience 2006;9:73–80. https://doi.org/10.1080/10284150600573660.

[63] Umezu T, Nagano K, Ito H, Kosakai K, Sakaniwa M, Morita M. Anticonflict effects of lavender oil and identification of its active constituents. Pharmacology Biochemistry and Behavior 2006;85:713–21. https://doi.org/10.1016/j.pbb.2006.10.026.

[64] De Araújo FYR, De Oliveira GV, Gomes PXL, Soares MA, Silva MIG, Carvalho AF, et al. Inhibition of ketamine-induced hyperlocomotion in mice by the essential oil of *Alpinia zerumbet*: possible involvement of an antioxidant effect. Journal of Pharmacy and Pharmacology 2011;63:1103–10. https://doi.org/10.1111/j.2042-7158.2011.01312.x.

[65] De Araújo FYR, Chaves Filho AJM, Nunes AM, De Oliveira GV, Gomes PXL, Vasconcelos GS, et al. Involvement of anti-inflammatory, antioxidant, and BDNF up-regulating properties in the antipsychotic-like effect of the essential oil of *Alpinia zerumbet* in mice: a comparative study with olanzapine. Metab Brain Dis 2021;36:2283–97. https://doi.org/10.1007/s11011-021-00821-5.

[66] Brundin L, Sellgren CM, Lim CK, Grit J, Pålsson E, Landén M, et al. An enzyme in the kynurenine pathway that governs vulnerability to suicidal behavior by regulating excitotoxicity and neuroinflammation. Transl Psychiatry 2016;6:e865–e865. https://doi.org/10.1038/tp.2016.133.

[67] Erta M, Quintana A, Hidalgo J. Interleukin-6, a major cytokine in the central nervous system. Int J Biol Sci 2012;8:1254–1266. https://doi.org/10.7150/ ijbs.4679.

[68] Zagrebelsky M, Korte M. Form follows function: BDNF and its involvement in sculpting the function and structure of synapses. Neuropharmacology 2014;76:628–638. https://doi. org/ 10.1016/j. neuropharm. 2013. 05. 029.

[69] Liapi C, Anifantis G, Chinou I, Kourounakis AP, Theodosopoulos S, Galanopoulou P. Antinociceptive properties of 1,8-cineole and β- pinene, from the essential oil of Eucalyptus

camaldu lensis leaves, in rodents. Planta Med 2007;73:1247–1254. https://doi.org/10.1055/s-2007- 990224.

[70] Tawata S, Fukuta M, Xuan TD, Deba F. Total utilization of tropical plants Leucaena leucocephala and *Alpinia zerumbet*. J Pestic Sci 2008;33:40–43. https://doi.org/10.1584/jpestics.R07-10.

[71] Tu PTB, Chompoo J, Tawata S. Hispidin and related herbal compounds from *Alpinia zerumbet* inhibit both PAK1-dependent melanogenesis and reactive oxygen species (ROS) production in adipocytes. Drug Discov Ther 2015;9:197–204. https://doi.org/10.5582/ddt.2015.01038.

[72] Tu PTB, Tawata S. Anti-obesity effects of hispidin and *Alpinia zerumbet* bioactives in 3T3-Li adipocytes. Molecules 2014;19:16656–16671. https://doi.org/10.3390/molecules191016656.

[73] Chompoo J, Upadhyay A, Gima S, Fukuta M, Tawata S. Antiatherogenetic properties of acetone extract of *Alpinia zerumbet* seeds. Molecules 2012;17:6237–6248. https:// doi.org/10.3390/molecules17066237.

[74] Lin LY, Peng CC, Liang YJ, Yeh WT, Wang HE, Yu TH, et al. *Alpinia zerumbet* potentially elevates high-density lipoprotein cholesterol level in hamsters. J Agric Food Chem 2008;56: 4435–4443. https://doi.org/10.1021/jf800195d.

[75] Chompoo J, Upadhyay A, Fukuta M, Tawata S. Effect of *Alpinia zerumbet* components on antioxidant and skin diseases-related enzymes. BMC Complementary. Alternative Med 2012;12:106. https://doi.org/10.1186/1472-6882-12-106.

[76] Cunha GH, Moraes MO, Fechine FV, Bezerra FAF, Silveira ER, Canuto KM, et al. Vasorelaxant and antihypertensive effects of methanolic fraction of the essential oil of *Alpinia zerumbet*. Vasc Pharmacol 2013;58:337–345. https://doi.org/10.1016/j.vph.2013.04.001.

[77] de Moura RS, Emiliano AF, de Carvalho LC, Souza MA, Guedes DC, Tano TRA. Antihypertensive and endothelium-dependent vasodilator effects of *Alpinia zerumbet*, a medicinal plant. J Cardiovasc Pharm 2005;46:288–94. https://doi.org/ 10.1097/01.fjc.0000175239.26326.47.

[78] Junior WAR, Gomes DB, Zanchet B, Schönell AP, Diel KAP, Banzato TP, et al. Antiproliferative effects of pinostrobin and 5,6-dehydrokavain isolated from leaves of *Alpinia zerumbet*. Rev Bras Farmacogn 2017;27:592–598. https://doi.org/ 10.1016/j.bjp.2017.05.007.

[79] Taira N, Nguyen BCQ, Tawata S. Hair growth promoting and anticancer effects of p21-activated kinase 1 (PAK1) inhibitors isolated from different parts of *Alpinia zerumbet*. Molecules 2017;22:132. https://doi.org/10.3390/molecules22010132.

[80] Upadhyay A, Chompoo J, Taira N, Fukuta M, Tawata S. Significant longevity-extending effects of *Alpinia zerumbet* leaf extracts on the life span of Caenorhabditis elegans. Biosci Biotechnol Biochem 2013;77:217–223. https://doi.org/ 10.1271/bbb.120351.