

The potencial anxiolytic and antidepressant effects of *Alpinia zerumbet* in elderly individuals

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 (Djernes, 2006). 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 adrenocorticotrophic 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-HT_{1A} 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 NF κ B 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].

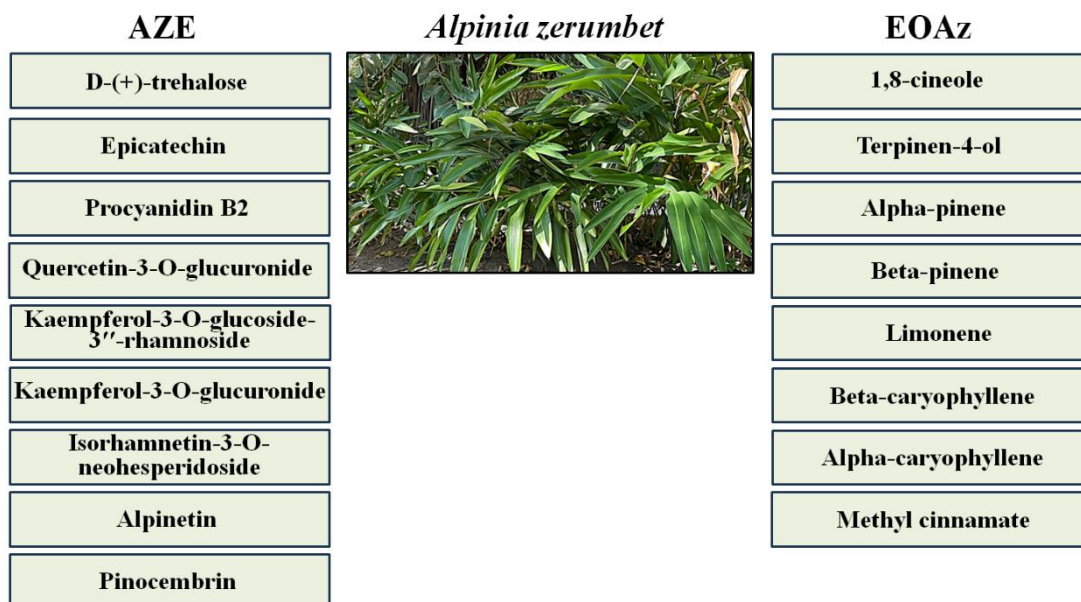


Fig. 1. *Alpinia zerumbet* illustrative diagram demonstrating the chemical compounds present in the hydroalcoholic fresh leaf extract of the plant and extracted from the essential oil. AZE - alpinia zerumbet hydroalcoholic fresh leaf extract, EOAz - alpinia zerumbet essential oil.

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, terpinen-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 *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, 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].

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

RESEARCH GROUP AND STUDY	YEAR	<i>Alpinia zerumbet</i> EFFECTS
Animal models		
Bevilaqua et al.,	2016	Depressive-like behavior
Roman Junior et al.,	2013	Depressive-like behavior
Bevilaqua et al.,	2016	Act through noradrenergic transmission
Murakami et al.,	2009	Anxiolytic-like behavior
Satou et al.,	2010	Anxiolytic-like behavior

Roman Junior et al.,	2013	Anxiolytic-like behavior
Murakami et al.,	2009	Increase locomotor activity
Roman Junior et al.,	2013	Increase antioxidant activity
De Araújo et al.,	2011	Increase antioxidant activity
De Araújo et al.,	2021	Increase antioxidant activity
De Araújo et al.,	2021	Decrease neuroinflammation
De Araújo et al.,	2021	Increase BDNF levels
Humans		
Teschke & Xuan	2018	Increase longevity
Teschke & Xuan	2018	Not induce toxicity

BDNF, brain-derived neurotrophic factor.

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 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].

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

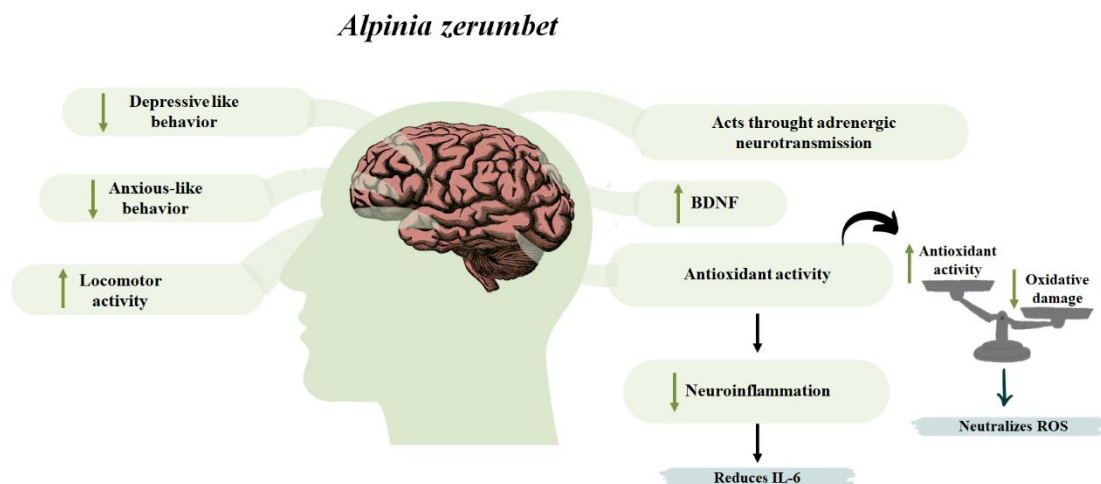


Fig. 2. Scheme summarizing the beneficial effects of *Alpinia zerumbet* that make it a promising medicinal plant for the treatment of depressive and anxiety disorders in elderly individuals. BDNF - brain-derived neurotrophic factor, IL-6 - interleukine-6, and ROS - reactive oxygen species.

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]. This action may contribute to the neuroinflammation decreasing since reactive species can cause the activation of NFκB, 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 *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]. Therefore, these antioxidant and anti-

inflammatory effects confirmed the potential of *Alpinia zerumbet* for treating psychiatric illnesses such as depression and anxiety (Fig. 2 and Fig. 3).

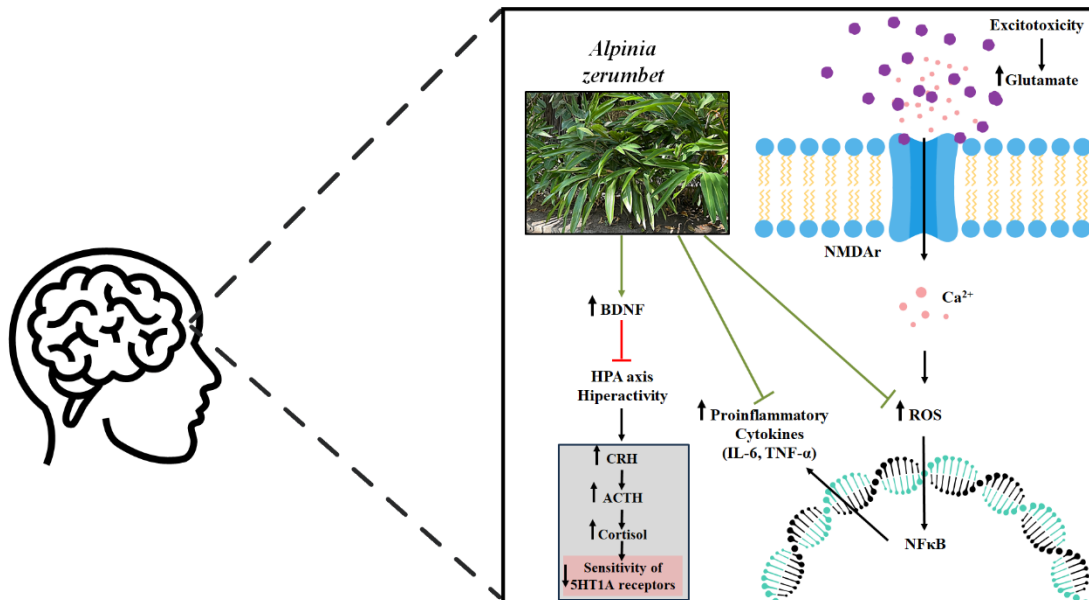


Fig. 3. Scheme summarizing the beneficial effects of *Alpinia zerumbet* that make it a promising medicinal plant for the treatment of depressive and anxiety disorders in elderly individuals. BDNF - brain-derived neurotrophic factor, IL-6 - interleukine-6, and ROS - reactive oxygen species.

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 *Alpinia zerumbet* increases the levels of this neurotrophin in the hippocampus of rats subjected to ketamine, a model of schizophrenia (Table 1) [65]. 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]. 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.

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