Promising Future of Herbal Medicine in the Treatment of Alzheimers Disease- A Review

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Abstract

The progressive neurodegenerative disease known as Alzheimer's disease (AD) is mostly linked to aging. Significant memory loss, aberrant conduct, personality changes, and a deterioration in cognitive function are the hallmarks of this debilitating illness. There is presently no cure for Alzheimer's disease, despite much study, and the effectiveness of the various treatments has been patchy. Addressing the increasing burden of Alzheimer's disease requires the development of therapeutic strategies to delay or stop the onset and course of the illness. With several molecules derived from Ayurvedic medicinal herbs presently undergoing clinical trials, this field of pharmacological development has shown great promise. The potential use of several Ayurvedic medicinal herbs and their derivatives in the treatment of Alzheimer's disease has been investigated scientifically.

Numerous phytochemical studies have shown a variety of advantageous chemicals in these plants, despite the fact that the exact mechanisms of action are still mostly unknown. These substances, which have a variety of pharmacological actions, include lignans, flavonoids, tannins, polyphenols, triterpenes, sterols, and alkaloids. These actions include antioxidant, hypolipidemic, anti-inflammatory, anti-amyloidogenic, and anticholinesterase properties. The phytochemistry, ethnomedical uses, and bioactive components of a variety of plants are highlighted in this article. It highlights how one of the oldest holistic healing systems in the world, Ayurveda, may be able to find successful treatment approaches for neurodegenerative diseases like Alzheimer's. The potential of Ayurvedic medicinal herbs and their constituents as innovative treatments for Alzheimer's disease is suggested by their encouraging pharmacological properties. These results provide promise for tackling the difficulties of this crippling illness.

Keywords: Alzheimer's, Neurodegeneration ,Toxicity, Herbal Medicine, Ayurveda, Clinical trials

INTRODUCTION:

Alzheimer's disease is a progressive neurodegenerative disorder that affects memory,reasoning, language, and behavior. It is the most common cause of dementia and is asignificant public health concern. It predominantly affects older adults, but rareearly-onset forms can occur.Alzheimer's disease was first identified in the early 20th century by Dr. AloisAlzheimer, who documented the case of Auguste Deter. His groundbreaking work laidthe foundation for subsequent research and the formalization of diagnostic criteria forthe disease. Currently, there are an estimated 50 million people worldwide living withAlzheimer's or related dementias, a number projected to rise to 152 million by 2050.The disease's epidemic proportions pose a significant global health challenge, withannual healthcare costs exceeding $1 trillion globally.The pathological hallmark of Alzheimer's disease includes the accumulation ofbeta-amyloid plaques and tau protein tangles in the brain..Beta-amyloid plaques areabnormal protein clumps that accumulate between nerve cells, disrupting intercellularcommunication. Tau protein tangles, on the other hand, form inside neurons, causingthem to become twisted and dysfunctional. These pathological changes lead to thedeath of nerve cells and a gradual loss of brain tissue, resulting in cognitive decline.While the precise etiology of Alzheimer's disease remains elusive, several risk factorshave been identified. Age stands as the most significant risk factor, with the risk ofdeveloping AD increasing significantly after the age of 65. Genetic factors, includingspecific gene mutations, can elevate susceptibility to the disease, especially in familialcases. A family history of Alzheimer's, particularly among first-degree relatives, mayalso increase

the risk. Furthermore, lifestyle factors such as cardiovascular health,physical activity, and diet have been suggested to influence the risk of developingAlzheimer's.[1-4]
Herbal treatments gave rise to the first pharmacopeias just around 200 years ago, and many of the manmade pharmaceuticals used today have their roots in the plant kingdom. Traditional treatments suffered a sharp decline as clinical and basic pharmacology were recognized as significant medical disciplines.However, research into herbal medicine is still ongoing for a number of conditions, including neurological and mental issues. This issue can be explained in a number of ways. First, patients are dissatisfied with traditional therapy; second, they believe that herbal therapies align with their personal values and beliefs; and third, patients want to have control over their medical decisions. Given the phytoconstituents' and extracted compounds' affinity for brain receptors, herbal remedies may be crucial for the treatment of neurologicalillness.Herbal medicines' general anti-inflammatory and antioxidant properties, along with their unique cholinesterase inhibitory impact, encourage their use in Alzheimer's disease treatment. The efficacy, safety, and affordability of herbal treatments are also factors contributing to their growing popularity. To evaluate the effectiveness of these herbal medicines alone or in the form of formulations for the therapy of AD, multicentric studies should be done. The usefulness of herbal drugs in treating Alzheimer's disease is discussed in the current review study.[5-8]

GINGER

Ginger has also been shown to prevent and treat degenerative diseases. Ginger's antioxidant and anti-acetylcholinesterase activities were examined in Alzheimer's patients The ability of ginger extract to scavenge free radicals in the DPPH experiment confirmed its antioxidant and anti-acetyl cholinesterase activities. When ginger extract is introduced to a solution, -amyloid inhibits butyrylcholinesterase and promotes cell viability. 6-gingerol reduces the expression of -amyloid, which is activated by ROS and nitrogen species, increases antioxidant enzyme expression, and restores glutathione. However, gingerol, contained in ginger, increased learning and memory in an Alzheimer's rat model and reduced oxidative stress and inflammation. This study found that high doses of ginger extract increased Nissl bodies and neurons, activated SOD and CAT, and decreased MDA, NF-B, and IL-1 levels. Another study found ginger to be effective in preventing and treating Alzheimer's disease in rats. It boosted T-maze test results, and lowered acetylcholinesterase activity in AD rats given 108 or 216 mg/kg ginger. Histological evidence shows that ginger consumption reduced amyloid plaques in AD animals.

Six-shogaol decreased astrogliosis and microgliosis in the brains of Parkinson's disease mice and enhanced NGF and synaptic molecule expression. The active component in ginger may lower inflammation, NGF levels, and synaptic growth in Alzheimer's disease (AD), according to this study. It rescued dopaminergic neurons from MPTP and MPP+-induced degeneration in an in vitro and vivo PD model. The substantia nigra pars compacta and stratum corneum protect dopaminergic neurons from oxidative stress by inhibiting iNOS and TNF-. Another investigation came to the same conclusion.[9,10]

BRAHMI

Brahmi, or *Bacopa monnieri* (Bm), is a perennial creeper medicinal plant found in the damp and marshy wetlands of Southern and Eastern India, Australia, Europe, Africa, Asia, and North and South America. In the Ayurvedic system of medicine, Bm is recommended for mental stress, memory loss, epilepsy, insomnia, and asthma. The bioactive phytochemicals present in this plant include saponins, bacopasides III, IV, V, bacosides A and B, bacosaponins A, B, C, D, E, and F, alkaloids, sterols, betulic acid, polyphenols, and sulfhydryl compounds, which may be responsible for the neuroprotective roles of the plant. Both in vitro and in vivo studies show that these phytochemicals have an antioxidant and free radical scavenging action by blocking lipid peroxidation in several areas of the brain. Bm acts by reducing divalent metals, scavenging reactive oxygen species, decreasing the formation of lipid peroxides, and inhibiting lipoxygenase activity.[11-14]

GINKGO BILOBA

Ginkgo biloba (Gb) has been in the spotlight primarily for its potential role in treating AD. Gb also appears promising as a therapeutic agent for several other chronic and acute forms of diseases. The main pharmacologically active groups of compounds are flavonoids and terpenoids. Almost all clinical studies use Gb extract that contains a combination of flavonoid glycosides, terpene lactones, and ginkgolic acids. Gb extract has shown beneficial effects in treating Alzheimer's, cardiovascular diseases, cancer, tinnitus, and other age-associated conditions. The suggested mechanisms of the Gb extract are its antioxidant effect, anti-platelet activating factor activity for vascular diseases, inhibition of β-amyloid peptide aggregation in AD, and decreased expression of peripheral benzodiazepine receptor for stress alleviation.

Gb is popular as a treatment for early-stage AD and vascular dementia. Gb extract reverses β-amyloid and NO-induced toxicity in vitro and reduces apoptosis both in vitro and in vivo. Treatment with Gb extract enhanced memory retention in young and old rats and improved short-term memory in mice.

Several studies indicate that ginkgo delays the progression of AD and is as effective as the cholinesterase inhibitors for treating AD. A modest improvement in cognitive function was observed in AD subjects in various randomized, double-blind, placebo-controlled trials. Gb extract also improves ADLs among AD individuals and is preferred over other AD medications because of its negligible adverse effects.[15-18]

TURMERIC

Turmeric is a flowering plant of the ginger family Zingiberaceae and is native to the Indian subcontinent and Southeast Asia. The bright yellow–orange color that this rhizome plant displays is mainly due to the polyphenolic compounds called curcuminoids. Turmeric is anti-inflammatory, antiseptic, and antibacterial and has long been used to treat a wide variety of conditions including liver detoxification, to prevent infection and inflammation, to balance cholesterol levels, to treat allergies, to stimulate digestion, and to boost immunity . The active constituents of turmeric are turmerone oil and water-soluble curcuminoids. Curcuminoids include curcumin, demethoxycurcumin (DMC), bisdemethoxycurcumin (BDMC), and cyclocurcumin. Curcumin is the principal curcuminoid whose anti-inflammatory property is associated with reduced risk of AD . In vitro studies revealed curcumin's ability to block lipid peroxidation and neutralize reactive oxygen species, which was several times more potent than vitamin E .

Oral administration of curcumin to aged mice with advanced plaque deposits resulted in a significant reduction in the plaque load. Curcumin also reduced inflammation, oxidative damage, and amyloid pathology in mouse models of AD . Direct injection of curcumin into the brains not only blocked further development of plaque but also reduced the plaque levels. Using animal models of AD, several studies have reported improvement in cognitive function in the curcumin-treated group. Researchers attribute the improvement to curcumin's ability to lower Aβ plaque levels as well as to its anti-inflammatory and antioxidant properties. Using an APP/PS1 double transgenic AD model, researchers examined the effect of two different doses of curcumin, including low (160 ppm) and high (1000 ppm), after administration for six months in the diet. While there was a significant cognitive improvement at both doses compared to the untreated group, the higher dose of curcumin produced greater cognitive improvement. Additionally, curcumin reduced the Aβ deposits, possibly by promoting autophagy. Owing to curcumin's low bioavailability, rapid gastrointestinal metabolism, and poor BBB penetration, several analogs of curcumin were tested for their bioavailability and for their effects on animal models of AD. While these derivatives produced different beneficial outcomes depending on the disease model, they were all better in improving cognitive function and reducing plaque pathology .

Curcumin also reverses cognitive impairments in various animal models of AD. Higher doses of curcumin are more effective compared to the lower doses regardless of the route of administration, and improvements in cognition were greater when curcumin was given in combination with piperine, which has numerous pharmacological effects and several health benefits, especially against chronic diseases . Metals such as copper, zinc, or iron may play a role in AD pathogenesis. These metals are concentrated in the AD brain and trigger amyloid aggregation or oxidative neurotoxicity . Curcumin forms strong complexes with metals and blocks metal-triggered Aβ aggregation, toxicity, and inflammation.

Contrary to animal studies, only a limited number of clinical studies have examined curcumin's effect on human cognitive functioning, and the results are inconclusive. Researchers are nearly unanimous in their opinion that a combination of curcumin with other dietary supplements, such as piperine, α-lipoic acid, *N*-acetylcysteine, B vitamins, vitamin C, and folate, has a synergistic effect and enhances its neuroprotective effects. Thus, improvements are needed, and future research should focus on ways to further increase curcumin's systemic bioavailability and improve its BBB permeability.

Turmeric is a rhizomatous herbaceous perennial plant ofthe ginger family, Zingiberaceae. Derived from therhizome and root, turmeric is used as a spice and coloringagent and in traditional medicine in Asia. The activeconstituents are thought to be turmerone oil and watersolublecurcuminoids, including curcumin . Curcuminis the principal curcuminoid and is responsible for theyellow color of the turmeric root . Turmeric isanti-inflammatory, antiseptic, and antibacterial and haslong been used in the Indian system of medicine to treata variety of conditions. Th is versatile spice helps detoxifythe liver, balance cholesterol levels, fi ght allergies, stimulatedigestion, and boost immunity . Epidemiologicstudies show a 4.4-fold lower incidence of AD inSoutheast Asian countries where turmeric is commonlyused as a dietary spice. Other studies indicate thatthe non-steroidal anti-inflammatory property of turmericis associated with a reduced risk of AD. Indeed,when fed to aged mice with advanced plaque depositssimilar to those of AD, curcumin reduced the amount ofplaque deposition. It reduced oxidative damageand reversed the amyloid pathology in an AD transgenicmouse. Direct injection of curcumin into thebrains of the mice with AD not only hampered furtherdevelopment of plaque but also reduced the plaque levels. AD symptoms characterized by inflammation andoxidation were also eased by curcumin's powerfulantioxidant and anti-inflammatory properties. Inaddition, a low dose of turmeric (160 parts per million, orppm) reduced proinflammatory cytokine levels that arelinked to the neuroinflammatory cascades involved inneuritic plaque pathogenesis. Curcumin's *in vitro*ability to inhibit lipid peroxidation and neutralize reactiveoxygen species may be several times more potent thanthat of vitamin E. Toxicity studies were conducted bythe National Cancer Institute by administering turmericoleoresin (organic extract of turmeric) in feed to groupsof male and female rats and mice for 13 weeks and2 years. Th ere were no acute or chronic clinical findingsrelated to toxicity in either rats or mice receiving 2,000,10,000, or 50,000 ppm of turmeric oleoresin .Owing to the promising fi ndings in animal models,clinical trials of oral curcumin supplementation inpatients with early AD are already under way. Inaddition, the results of a six-month randomized, placebocontrolled,double-blind, clinical trial of curcumin in 27patients with AD found that oral supplementation withup to 4 g/day of curcumin was safe . Larger controlledtrials are needed to determine whether oral curcuminsupplementation is efficacious in AD [19-22]

SHANKHPUSHPI (*CONVOLVULUS PLURICAULIS*)

Various species for Shankapushpi, including *Convolvuluspluricaulis*(CP), *Convolvulus microphyllus*, *Evolvulusalsinoides*, and *Clitoriaternatea*(CT), have been described.Shankhpushpi is a common plant in India, wherethe whole plant is used in various formulae as a nervinetonic for improvement of memory and cognitive function

A wide range of secondary metabolites, includingtri terpenoids, flavonolglycosides, antho cyanins, andsteroids, has been isolated and may be responsible forShankhpushpi's nootropic and memory-enhancing propertiesin addition to other pharmacological activities . It is believed that Shankhpushpi calms the nerves byregulating the body's production of the stress hormones,adrenaline, and cortisol. It is also recom mended fornervous disorders such as stress, anxiety, mental fatigue,and insomnia. The ethanolic extract of CP andits ethyl acetate and aqueous fractions significantlyimproved learning and memory in rats. Th eethanolic extract of CP also possesses significant antioxidantactivity when tested *in vitro*. Anethanolic extract of the whole plant, when administeredto cholesterol-fed gerbils, reduced serum cholesterol,LDL cholesterol, triglycerides, and phospholipidssignificantly . A dose-dependent enhancement ofmemory was observed in mice that were administeredextracts of CP. Similarly, administration of CP extractsfor 7 days enhanced memory in aged mice. Hippocampalregions associated with the learning and memoryfunctions showed a dose-dependent increase inacetylcholine esterase activity in the CA1 and CA3 areawith CP treatment. Specifically, administration ofaqueous root extract of CT to neonatal rat pups resultedin improved retention

and spatial learning performance,indicating the memory-enhancing property of CT. Inaddition, a significant increase in acetylcholine contentwas observed in the hippocampi of CT-treated rats incomparison with age-matched controls. Increase in acetylcholinecontent in the hippocampus may be the neurochemicalbasis for their improved learning and memory. Young adult rats intubated with aqueous rootextract of CT showed a significant increase in passiveavoidance learning and retention. A significant increasein dendritic intersections, branching points, anddendritic processes arising from the soma of neurons inthe amygdale region in CT-treated rats was observed incomparison with age-matched saline controls, suggestingthat CT enhances memory by increasing the functionalgrowth of neurons .[23-26]

GUGGULU

Guggulu is an oleogum resin exuding from the cracksand fi ssures in the bark or from incisions from severaldiff erent plant species, including *Commiphoramukul*, *C.molmol*, *C. abyssinica*, *C. Burseraceae*, and *C. whighitii*.Th e oleogum resin of guggulu is a mixture of 30% to 60%water-soluble gum, 20% to 40% alcohol-soluble resins,and about 8% volatile oils. Water-soluble constituentsinclude mucilage, sugars, and proteins. Alcohol-solubleconstituents include the commiphoric acids, commiphorinicacid, and the heerabomyrrhols. Among thevolatile constituents are terpenes, sesquiterpenoids,cuminic aldehyde, eugenol, and the ketone steroids ZandE-guggulsterone, and guggulsterols I, II, and III.Guggulu also contains ferulic acids, phenols, andother non-phenolic aromatic acids that are potentscavengers of superoxide radicals and could potentiallybe of importance for the treatment of AD and otheroxidative stress-related disease . Th e gum resinhas been used for thousands of years in the treatment ofarthritis, inflammation, obesity, and disorders of lipidmetabolism.In animal models and in humans, administration ofguggululipid is reported to significantly lower both serumLDL cholesterol and triglyceride levels. Insightinto the mechanism of action for the hypolipidemicactivity was provided by the demonstration that gugguluis an effective antagonist of the bile acid receptorfarnesoid X receptor. Epidemiologic and biochemicaldata suggest a link between cholesterol, APPprocessing, and AD. Th ese studies indicate thatthere is a decreased prevalence of AD associated with theuse of cholesterol-lowering drugs. Decreasedneuronal cholesterol levels, in turn, inhibit the betaamyloid-forming amyloidogenic pathway, possibly byremoving APP from cholesterol and sphingolipid-enrichedmembrane microdomains. Th ese intriguingrelationships raise the hopes that cholesterol-loweringstrategies may influence the progression of AD . Arecent study demonstrated that guggululipid has a significant protective effect against the streptozotocin-inducedmemory deficit model of dementia; the effect can beattributed to its cholesterol-lowering, antioxidant, andanti-acetylcholine esterase activity. Th ese observationssuggest guggululipid as a potential anti-dementia drug.[27-30]

NUTMEG

Nutmeg (Myristica fragrans) It is a member of the Myristicaceae family. It's used to treat mental disorders, digestive problems, leukaemia, body aches, vomiting, tachycardia, dizziness, and memory problems. It has antidepressant, antioxidant, and antibacterial properties. Nutmeg N-hexane extract was given orally to young and old mice at three dose levels (5, 10 and 20 mg/kg p.o.) for three days. At 5 mg/kg, this medication was found to be helpful in reversing scopolamine and diazepam-induced learning and memory deficits. This study established the efficacy of Myristicafragrans in the treatment of AD and memory loss. Guduchi (Tinospora cordifolia) It is a member of the Menispermaceae family and has memory-enhancing qualities in both normal and memory-deficient animals. Choline supplementation improves cognitive performance by stimulating the immune system and enhancing acetylcholine production. It is known as a learning and memory booster in Ayurveda. The use of an aqueous extract of guduchi roots improved verbal learning and logical memory.[31-34]

DRUMSTICK

Drumstick tree (Moringa oleifera) It is a member of the Moringaceae family. Its leaf extract contains antioxidant vitamins C and E, which help to improve cognition in Alzheimer's patients It contains nootropic properties and can help with stress in Alzheimer's patients . It affects monoamines, which have a role in memory. According to a rat study, Moringa oleifera reduces the severity of colchicine-induced AD via altering monoamine levels such as norepinephrine, dopamine, and serotonin. [35-38]

AMLA

Amla (Emblica officinalis) It is a member of the Euphorbiaceae family. In a dose-dependent manner, it showed a considerable improvement in memory retention in young and old rats. It has an important function in the treatment of memory deficits and AD as a memory enhancer and reversal of memory deficiencies . In a study, the memory-enhancing effect of piracetam when combined with amla and turmeric against aluminum-induced cognitive impairment and oxidative damage in rats was investigated. For six weeks, rats were administered 100 mg/kg of aluminium chloride orally. Rats were given amla (100 mg/kg, p.o.), curcumin (100 mg/kg, p.o.), and piracetam (200 mg/kg, i.p.) at the same time for 6 weeks. On days 21 and 42 of therapy, memory was assessed using elevated plus maze task paradigms and Morris water maze tests. Rats were slaughtered on day 43 of treatment to determine the amount of oxidative damage. In rats treated with Emblica officinalis (100 mg/kg, p.o.), curcumin (100 mg/kg, p.o.), and piracetam (200 mg/kg, i.p.), oxidative stress was greatly reduced and memory was significantly improved compared to rats treated solely with piracetam (200 mg/kg, i.p.). Amlacould be used to treat memory loss, it has an antioxidant and memory enhancer properties.[39-42]

LIQUORICE

Liquorice (Glycyrrhiza glabra) It is a member of the Fabaceae family and contains coumarins, isoflavonoids, saponins, flavonoids, and stilbenoids, which are used to treat Alzheimer's disease . Gastric ulcers, lung congestion, hoarseness, and throat difficulties are all treated by liquorice . Liquorice has been shown to improve memory in scopolamine-induced dementia . Liquorice has been shown to improve memory in mice . Another study found that giving a 1-month-old albino rat orally fed Glycyrrhiza glabra plant extract for 6 weeks increased memory and learning capacity. Furthermore, a study found that Glycyrrhizainflata extract, a distinct species of glycyrrhiza, strongly reduced Aβ aggregation and radical-scavenging activities.[43-46]

SAFFRON

Saffron is a crimson-colored spice widely cultivated in Iran, India, and Greece. In addition to being used in the textile and cosmetic industries, saffron also boasts a variety of medicinal properties, including antioxidant and anti-inflammatory activities.

Studies show that this supplement can improve cognitive function in patients with mild to moderate Alzheimer’s at the same rate as prescription drugs donepezil or memantine, with the bonus of fewer side effects. Saffron can likely treat patients with dementia because it can inhibit the aggregation and deposition of beta-amyloid plaques, but this theory still needs confirmation.[47-50]

CONCLUSION

The pharmaceutical industry is facing serious challenges asthe drug discovery process for neurodegenerative diseasesis becoming extremely expensive, riskier, and criticallyinefficient. A significant shift from a single-target to amulti-target drug approach, especially for chronic andcomplex disease syndromes, is being witnessed.Approaches based on reverse pharmacology (from theclinic to the bedside) also off er efficient developmentplatforms for herbal formulations. The Ayurvedic systemof medicine has garnered increasing recognition inrecent years with regard to diet and treatment options.Early development of Ayurvedic herbal supplementsrequired only anecdotal or epidemiologic information (orboth) without an understanding of the mode of action.. It might be worth pointing outthat, while Ayurvedic therapeutics has been prescribedfor centuries for neurodegenerative diseases (includingdementias), only recently have there been Western,mechanistic studies on AD; however, these mechanisticstudies point to the same mechanisms addressed by theAyurvedic therapeutics (for example, increase in nervegrowth factors and neurotrophic factors and reduction ininflammation and oxidative damage), providing strongsupport for herbal therapy for AD. It is hoped thatthe strong knowledge base of Ayurveda coupled withcombinatorial sciences and high-throughput screeningtechniques will improve the ease with which Ayurvedicproducts and formulations can

be used in drug discoverycampaigns and development process, thereby providingnew functional leads for AD and other age-associatedneurodegenerative diseases.

As a result, herbal therapy is expected to slow the progression of Alzheimer's disease and alleviate its symptoms. Patients with Alzheimer's disease and memory problems may benefit from herbal therapy. There is a lot of research going on around the world to find an effective treatment for Alzheimer's disease. According to this study, herbal therapy appears to be a promising option for treating Alzheimer's disease. One of the main advantages is that, as compared to pharmaceutical drugs, they have low toxicity. The use of various herbal products is becoming increasingly popular. Because multiple studies have shown that using synthetic medications has negative side effects, there is a need for an alternate source of drugs with minimal or no side effects. Future scope Alternative medicine has been used since ancient times, and several extracts of medicinal plants and herbal combinations have shown promise in the treatment of Alzheimer's disease. Pharmacologically active phytoconstituents should be extracted, identified, and carefully tested.

Additionally, adopting a healthy lifestyle plays a critical role in managing Alzheimer’s symptoms. Regular physical activity, a balanced diet, socialization, and cognitive engagement are recommended. The combination of these can help slow down the progression of symptoms and enhance quality of life.

Lastly, for those exploring natural treatment avenues, it is also worth considering treatment optionswhich combine physical and cognitive therapy to help Alzheimer’s patients slow disease progression and maintain autonomy for longer.

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