Medicinal potential of *Cullen corylifolium* in ageing and ageing related diseases

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ABSTRACT

Cullen corylifolium is a tropical medicinal plant of the Fabaceae family, generally known as Babchi/Bakuchi in various regions of Asia. *Cullen corylifolium* is a traditional phyto-therapeutic plant of China used to manifest various pathological conditions since ages, possesing round and dark brown seeds with a rough texture. Cullen corylifolium has been previously reported to possess various properties such as antioxidant, anti-inflammatory and can be used as a solution to treat various ageing diorders. Despite the fact that this medicinal plant carries various therapeutic actions, the therapeutic potential of Cullen corylifolium seed is yet to be studied. Whereas, the seeds of *Cullen corylifolium* have previously been reported to contain various phytoconstituents including; coumarins, bavachin, bavachinin and flavonoids which may be utilised to study various geriatric ailments such as diabetes, cardiovascular diseases, osteoporosis, neuroprotection and obesity. This review seeks to assess the therapeutic effects of phytoconstituents present in the seed of *Cullen corylifolium on* the geriatric diseases. This review contains the mechanism of 5 phytocompounds (bavachinin, bavachin, bavachalcone, isobavachalcone, and neobavaisoflavone) present in Bakuchi seeds that have previously been reported for their anti-ageing potential and these phytocompounds were further detailed searched using scientific literature from Pubmed, Pubchem and Google Scholar. The scientific literature studied revealed that the seeds of *Cullen corylifolium* also possess anti-inflammatory and anti-oxidative potential that can be used further to intervene geriatric illness. As a result, this review will be beneficial in providing information

for future research and in discovering the potential drug for treatment of ageing associated diseases.

INTRODUCTION

The Fabaceae and Leguminosae family of plants is widely distributed with 765 genera and about 20,ooo known species. The species and genera belonging to this family are reported for their traditional medicinal potential and contain various phytocompounds, a very few of them are bavachinin, bavachin, and bavachalcone [1]. Plants from *Cullen* genera had been given importance due to phytotherapeutic action they showed. One of such important plants is *Cullen corylifolium,* it is a medicinal plant belonging to Fabaceae family and cullen genera ,is an erect annual herbaceous plant, vernacular to north-east tropical Africa, tropical Asia and Southern Arabian Peninsula [2]. Length of this plant ranges from 0.6 m to 1.2 m in height. It has grooved stem and leaves are 3.8*2.0-5.0 cm long and hairy. The petioles are spotted and have hairy exteriors. Thick axillary single racemes containing 10 -30 flowers are present in the plant. The fruit pods are 5mm in length and are ovoid in shape. Seeds are flattened and have an aromatic smell [3]. Additionally, the cultivation and climatic conditions for this plant are not specific. The crops can be cultivated successfully on various types, from sandy loam to black cotton soils, in subtropical climates with low to medium rainfall. Fertile red loamy soils with a pH between 6.5 to 7.5 and soils rich in organic matter content are ideal for cultivation. [4] .

Classification of *Cullen corylifolium*

Classification is the structural grouping of organisms into groups on the foundation of relationships among them. According to the ICBN (International Code of Bionomial Nomenclature), the stratum for the classification of plants is Kingdom, Clade, Order, Family, Sub-family, Genus, and Species, (see table 1).

Table 1:Scientific Classification of *Cullen corylifolium*

Scientific Classification of *Cullen corylifolium*	
Cullen corylifolium Kingdom	Plantae
Cullen corylifolium Clade	Tracheophytes
Cullen corylifolium Clade	Angiosperms
Cullen corylifolium Clade	Eudicots
Cullen corylifolium Order	Fabales
Cullen corylifolium Family	Fabaceae
Cullen corylifolium Sub Family	Faboideae
Cullen corylifolium Genus	*Cullen*
Cullen corylifolium Species	*Cullen corylifolium*
Bionomial Name	
Cullen corylifolium	
Trade Name	
Bakuchi	

Characteristics of *Cullen corylifolium*

It has been previously reported that *Cullen corylifolium* plant shows remarkable healing effects against kidney and spleen meridians .The plant revealed cytotoxic and antibacterial qualities as well as being cardioactive. It has a pigmenting purpose. The plant also showed cytotoxicity towards worms and tumours [5],[6]. Indigenous medical systems utilise P. corylifolia seeds to treat a variety of illnesses [7]. Furthermore, *Cullen corylifolium* contains a single elongated seed which is perennial, and mature in the month of november, heralding it's outrageous therapeutic properties.The seedshave laxative, diuretic, aphrodisiac, and anti-helminthic properties. Presence of the phytocompounds (bavachinin, bavachin, bavachalcone, isobavachalcone, and neobavaisoflavone), reports the usage of bakuchi seeds for numerous diseases namely skin diseases, cardiovascular diseases, diabetes, neurological disorders and geriatric diseases [8]. Seed of *Cullen corylifolium* have different characteristics ,(see table 2).

Table 2 : Characteristics of bakuchi seed

Sr. no.	Organoleptic characters	Observation
1	Odour	Aromatic odour
2	Taste	Bitter taste
3	Colour	Brownish Black
4	Touch	Rough

Uses of *Cullen corylifolium*

Cullen corylifolium, has been extensively used in traditional therapeutics, primarily Ayurveda ,traditional Chinese medicine and folk medicine. In ayurveda, bakuchi holds an important place due to its therapeutic action against various skin disorders like leucoderma, psoriasis, dermatitis and eczema [9]. Various compounds of bakuchi have been reported for their therapeutic actions such as psoralen (a photosensitizing compound), is ground into a paste for its application, resulting in depigmented skin. Usually people attend traditional medicine for the first time and these traditional practices have been crucial in the treatment of chronic ailments such as the fruit-derived volatile oils (from the extract of *Cullen corylifolium*) excite the voluntary muscles when present in high quantities and irritate the skin and mucous membranes [10],[11],[12]. When coupled with other herbs, also *Cullen corylifolium* extracts have been utilised in many of the herbal formulations to treat psoriasis and various other skin disorders [13].

The Demographic People's Republic of Korea has a deep history of employing traditional medicine and is one of the dignitary in merging traditional medicine with allopathic treatments to offer care and maintain health, however the use of primary traditional medicine in primary heath care and universal health care is increasing [14].*Cullen corylifolium* has been a part of Traditional Chinese medicines(TCM). According to TCM theory, Bakuchi is used to strengthen tendons and bones and restore kidney function. It is also recommended for illnesses like lower back discomfort, infertility, joint pain, and impotence.

Cullen corylifolium has been used in various folk medical traditions all over many countries, apart from formalised medical systems like Ayurveda and TCM. The local communities of the area where the herb grows, are naturally aware of its medicinal properties. Bakuchi is utilised for its benefits for treating various medical conditions because of its anti-inflammatory and analgesic

effects including pain reduction and inflammation caused by arthritis, rheumatism and other musculoskeletal disorders.

Cullen corylifolium IN AGEING AND AGEING RELATED DISEASES

*A*geing is the steady reduction in physiological function, which is a typical and inevitable process [15]. Ageing is caused by a number of changes including behavioural, environmental, and genetic changes. Researchers reported three factors that drive ageing:1) Hallmark's level with increasing age. 2)Rapid pace of ageing through experimental focus on the hallmarks 3) Possibility of declining ageing through therapeutic interventions [16]. Previously, 12 hallmarks of ageing were described : Genomic instability, Epigenetic alterations, Deregulated nutrient-sensing, Cellular senescence, Dysbiosis, Telomere attrition, Stem cell exhaustion, Mitochondrial dysfunction, Altered intracellular communication, , Disabled macroautophagy, Chronic inflammation and Loss of proteostasis, Fig.(1).

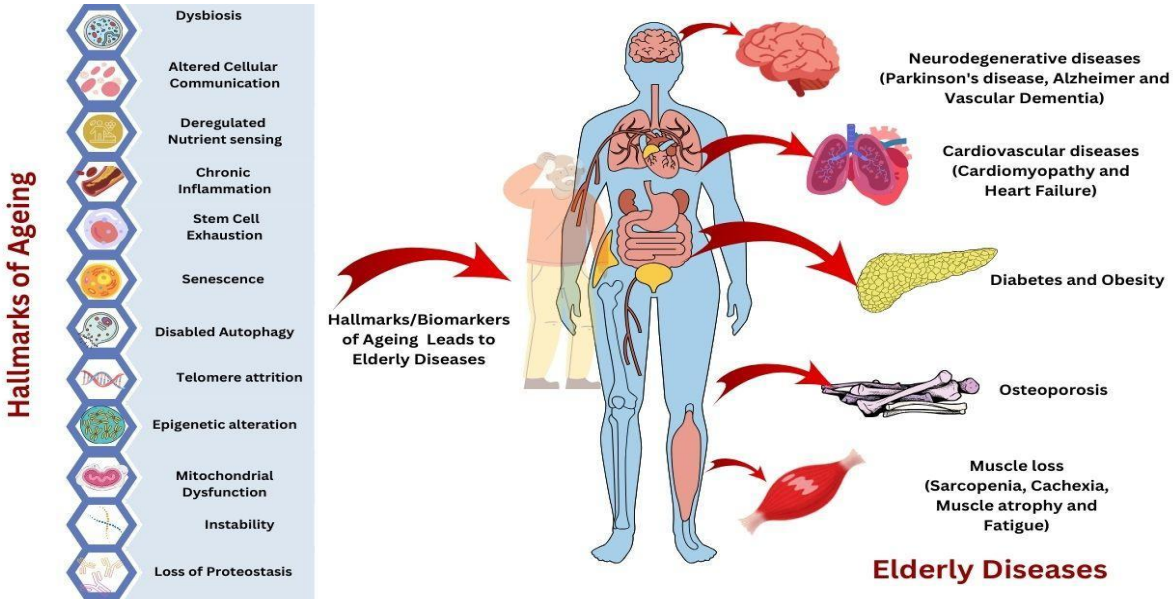

Figure 1: Here are the 12 proposed hallmarks of the ageing : Genomic instability, Epigenetic alterations, Deregulated nutrient-sensing, Cellular senescence, Dysbiosis, Telomere attrition, Stem cell exhaustion, Mitochondrial dysfunction, Altered intracellular communication, , Disabled macroautophagy, Chronic inflammation and Loss of proteostasis are shown to be responsible for geriatric diseases(neurodegenerative diseases, cardiovascular diseases, diabetes, obesity, osteoporosis and muscle loss conditions).

Ageing is also characterised by variations in hormone levels and *Cullen corylifolium* alleged capacity to regulate hormone synthesis may support an individual's general health and vigour as they age. *Cullen corylifolium* has also drawn attention recently due to its anti-aging properties. In spite of the fact there hasn't been much scientific research done on this specific subject, there are a number of achievable methods that bakuchi could affect aging-related processes. *Cullen*

corylifolium possesses various bioactive compounds including phenolic acids, coumarins, and flavonoids, which have antioxidant mechanisms [17]. Antioxidants assist the body's defence against harmful free radicals by lowering oxidative stress, which is linked to age-related illnesses. Bakuchi is globally utilised for its anti-inflammatory properties, which may lessen inflammation and its damaging effects on organs and tissues, encouraging ageing in a healthy manner. Bakuchi is typically used to strengthen tendons and bones, which suggests that bakuchi could help maintain bone and joint health with increasing age [18]. Bakuchi has also shown support for neuronal health, guard against oxidative stress and inflammation in the brain, protect consequent function and lowers the chances of age related neurodegenerative illness function, generating proinflammatory factors and the potential for systemic inflammation that leads to ageing-related illnesses.Various phytocompounds of bakuchi like bavachinin, neobavaisoflavoone, bavachalcone, bavachin have been shown in recent pharmacological research to have a various pharmacological activities and potential to improve disorders associated with ageing. *Cullen corylifolium* flavonoids are reported for their microsomal enzyme inhibitory potential, specifically in vitro experiments. For example, cholesterol acyltransferase enzyme responsible for lipoprotein production catalyses in the liver and the esterification of cholesterol in the intestine was suppressed by isobavachalcone and bavachin [19].

AGEING RELATED ILLNESS

All age-associated disorders are caused by multiple biochemical and genetic pathways that are mediated by the physiological process of ageing. These pathways are directly tied to longevity. overly from the past few decades, there has been a notable increment in human life expectancy,, but this has not been matched by a corresponding improvement in healthspan. Resultant, numerous ageing mechanisms have been discovered, chief among them being telomere shortening, cellular senescence, and genomic instability. Numerous age-related illnesses, such as cancer, cardiovascular disease, neurological diseases, immune system problems, and musculoskeletal disorders are all influenced by ageing [9]. In this review paper, we are focusing on anti-aging effects of flavonoids on ageing related illness, such as cardiovascular disorders, diabetes and obesity, osteoporosis, neurological disorders and discussing the effects of active ingredients of bakuchi of geriatric diseases (Table 3).

Table 3: Phytocompounds of *Cullen corylifolium* regulate different pathways by their anti-aging mechanism.

Disease and condition targets	Bakuchi action
Cardiovascular Function Regulation	Bavachalcone enhances the expression of EPO and operates AMPK to improve cardiovascular function [20].
Diabetes and obese intervention	Bavachinin activates PPARs to lower obesity and insulin resistance[21].
Anti -Inflammatory Action	Bavachinin hinders theHIF-1α.(hypoxia) signal transduction pathways [26].
Improve Osteoporosis	Flavonoids manage Runx2 ,Osx, Wnt and ERα/β to enhance osteoblast differentiation[30].
Neurodegenerative illness: (PD),(VD) and (AD) .	Flavonoids promote Nrf2, PPARγ , triggers EPO and anti-inflammatory activities to have neuroprotective advantages [38].

Cardiovascular Function Regulation

The growing age leads to stunted degree of inflammation and higher oxidative stress leads to lower degree of inflammation and greater oxidative stress in the cardiovascular system. These changes consist of endothelial dysfunction, stroke, cardiac diastolic dysfunction and others. This involves AMPK pathway, MnSOD and PGC-1α genes .Bavachalcone has also been reported to protect endothelial cells by enhancing the action of AMPK and the impression of MnSOD and PGC-1α genes, lowering the oxidative stress and enhancing biogenesis of mitochondria [20]. Additionally, scientist reported that bavachalcone enhanced neovascularization (In rat model of ischemia hind limb, 14 days treatment of oral bavachalcone induced the neovascularization and restored microcicrculation) and the differentiation of (EPC's) via AMPK pathway(In rats treated with bavachalcone, both the amount of EPCs and(EPO in the blood were increased) Fig (2).

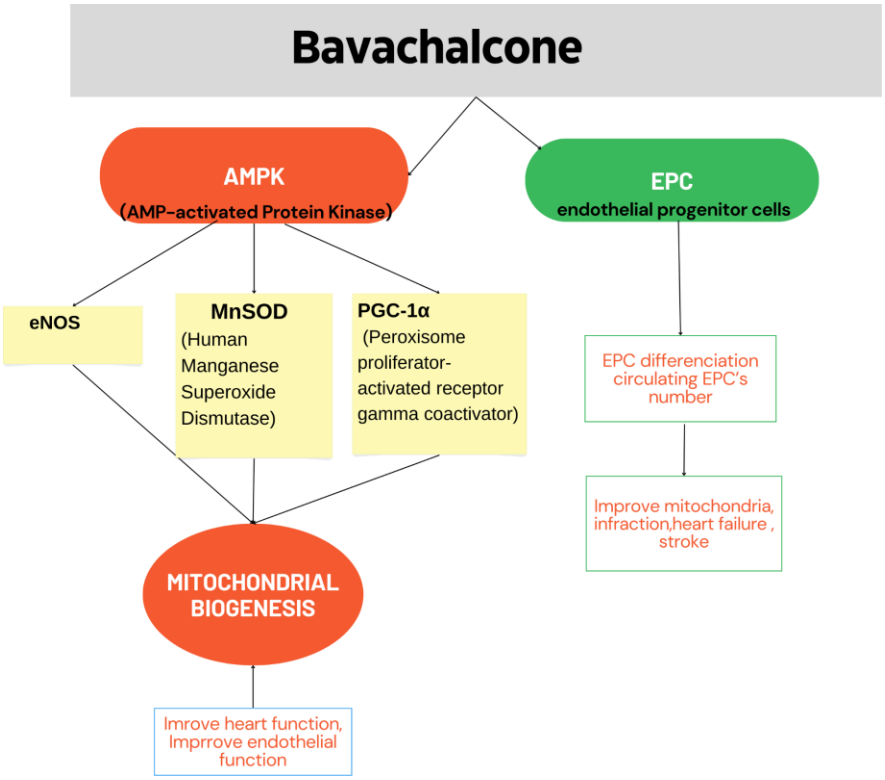

Figure 2: The schematic of bavachalcone, which increases the expression of EPO and operates AMPK to improve cardiovascular function.

Diabetes and obese intervention

Diabetes has high chances of occurrence in elderly due to increased oxidative stress and inflammation brought on by age. Scientist reported that bavachin enhanced theexpression of PPARγ gene, that increases accumulation of lipids in 3T3-L1 cells at 8th day of differentiation , proposing that bavachin could have healing properties for type II diabetes [21]. Another PPARγ agonist Bavachinin, it has S and R configurations. Recently, in vivo researches have shown that bavachinin has the ability to lower blood glucose levels without weight gain or causing any harm to the liver. Fig (3)

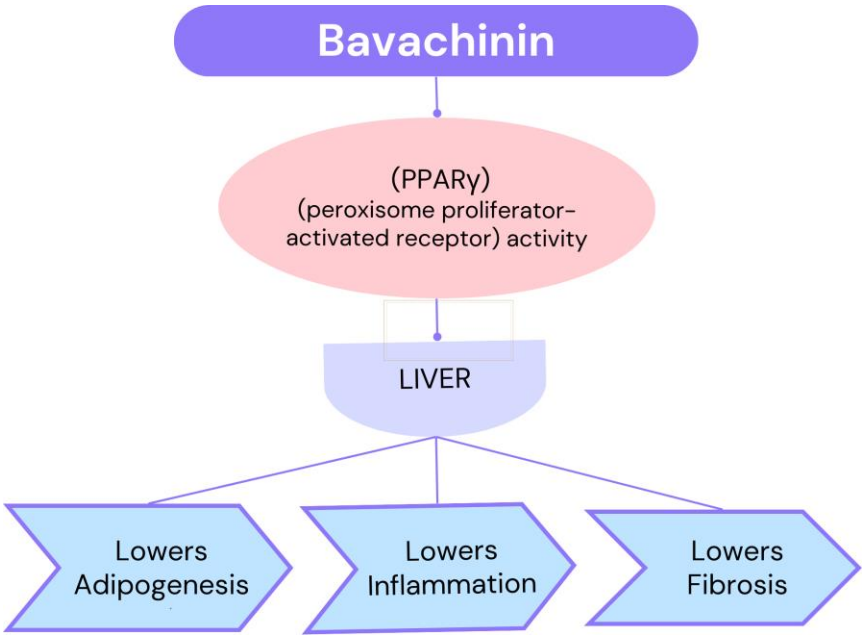

Figure 3: The flow chart showing how bavachinin activates PPARs(peroxisome proliferator-activated receptor) to lower obesity and insulin resistance.

Anti -Inflammatory Action

Cullen corylifolium is a customary anti-ageing medical herb and the plant's defiance to "inflammaging" has become an interesting area of studying anti-ageing. Bavachinin has been addressed to have anti-inflammatory effects [22]. The primary oxygen sensor in cells is HIF-1α and is obligatory for controlling how cells reply to oxygen level changes.Bavachinin (under hypoxic conditions) reduced activity of HIF-1α in a dose-dependent mode and hindered (energy metabolism-related genes) hexokinase 2 and Glut 1, HIF-1 regulated transcription [23]. Inflammation and the mitochondrial metabolism have intricate networks with the transcription factor HIF-1α [24].The expression of HIF-α,IL-1β and other HIF-α dependent genes was reduced by PKM2 (pyruvate kinase M2). When PKM2 is activated by LPS (lipopolysaccharide), it binds directly to the IL-1β promoter and contrive a complex with HIF-1α.Moreover,researchers found that the development of succinate and glycolytic reprogramming activated by LPS, were blocked by stimulated PKM2 [25]. Succinate, that is generated by LPS stabilises HIF-1 alpha, which guides the initiation of the IL-1 beta (proinflammatory cytokine) [24].

M1 macrophages mediate the obesity-interrelated inflammation in HFpEF , that is fascinated by the HIF-1α. M1 macrophages also stimulates the articulation of the collagen, thrombospondin, NADPH, pro-α2(I) and CTGF and produces IL-6, IL-1β (proinflammatory cytokines). Therefore, ,bavachin suppresses the effect of HIF-1α (below the hypoxic circumstances) that resists the provocative action [26] (Figure 4).

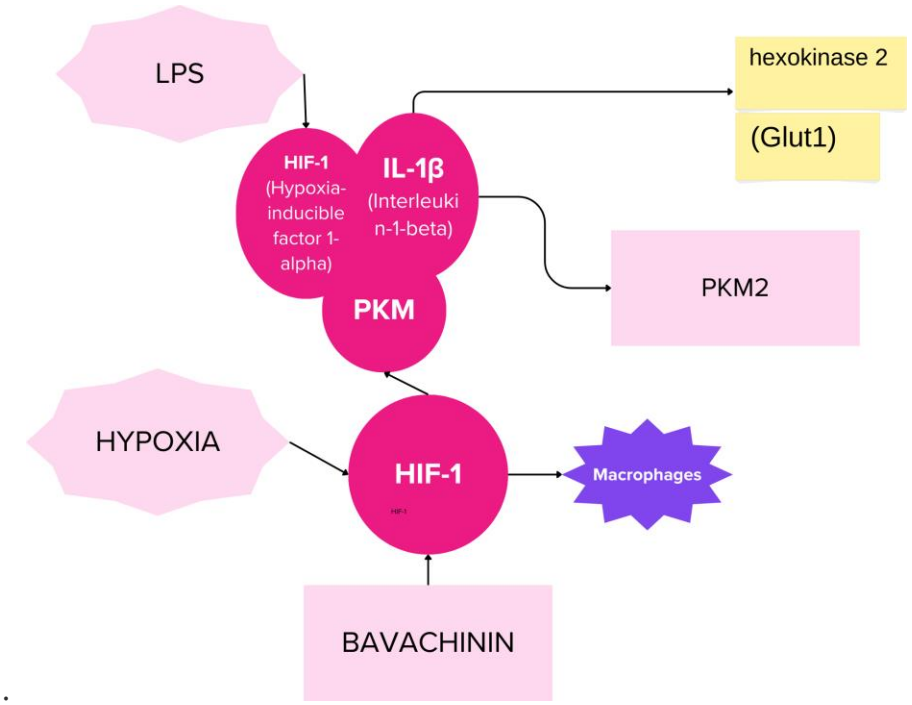

Figure 4:Illustrates how bavachinin inhibits the HIF-1 alpha signal transduction pathways in the anti-inflammatory.

Improve Osteoporosis

Osteoporosis and ageing are highly coorelated, which affects both women and men. Ageing results in deterioration of bone structure, function and composition which causes osteoporosis. Osteoporesis is explained as worsening in bone density, with enhancement of fragility fractures [27]. The previous studies showed that : (1) Bone cell DNA damage [28] ;(2) Osteoporosis is induced by excessive osteoclast activity induced by ageing ,which causes inflammation [29].

Cullen corylifolium is extensively used in China to treat osteoporosis, osteomalacia, and fractures. According to researchers, pure oestrogen antagonists like ICI-780,182 totally inhibit the triggering of oestrogen receptors, but neobavaisoflavone, isobavachalcone, bavachin enhance ERα and ERβ.

Additionally, neobavaisoflavone and isobavachalcone simuntaneously increased osteoblast proliferation. In vivo research with use of an ovariectomy-induced model of bone loss, bavachin reduced loss of bones by enhancing pathway of Wnt signalling [30].The Wnt signalling system managed cell destiny and stimulate the movement of BMSC's to the osteoblasts from the adipocytes [31]. Simultaneously, neobavaisoflavone significantly enhanced matrix proteins that are bones specific like OCN, Col-I and BSP as well as the genesis of bone nodules. It also significantly stimulated ALP activity in osteoblasts in a concentration-dependent way. Neobavaisoflavone also enhanced the expression of mRNA of the transcriptional factors such as

Runx2 and Osx along a p38-dependent signalling pathway, which had osteogenic effects [32] (Figure 5).

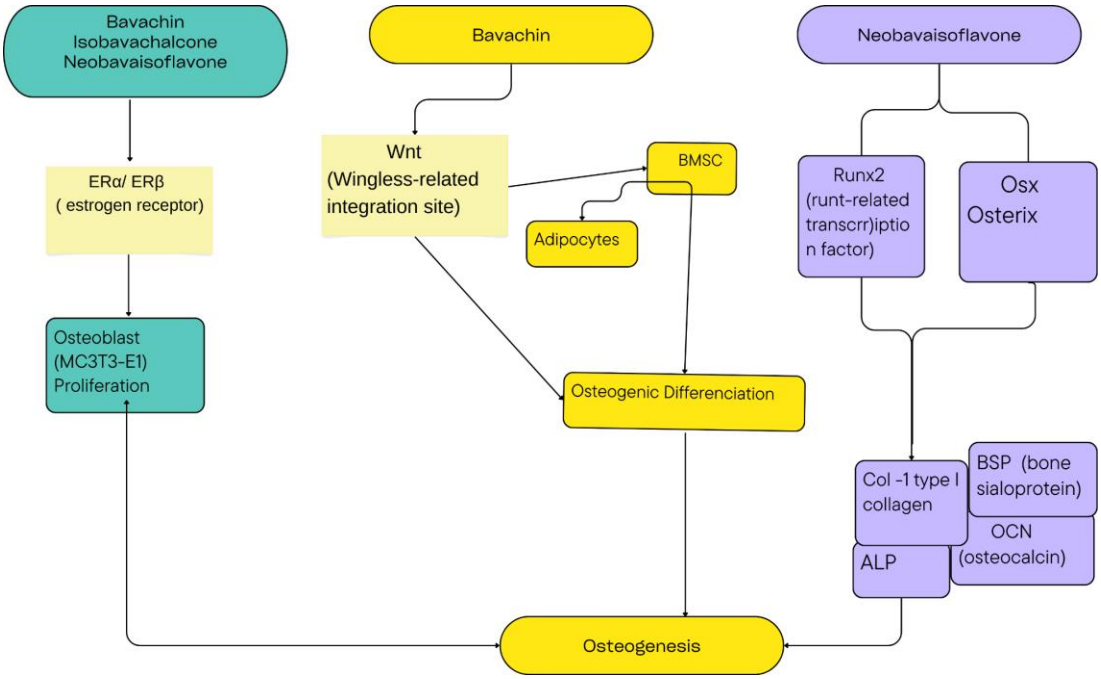

Figure: 5 The schematic diagram illustrating how various flavonoids regulate Runx2,, Wnt, Osx , ERalpha/beta to promote osteoblast differentiation

Neurodegenerative illness

The exceptional risk factor for neurodegenerative illnesses is ageing. Worldwide, millions of people are impacted by ischemic stroke, Parkinson's disease , Alzheimer's disease and Vascular dementia. At present, *Cullen corylifolium* with anti-ageing properties is being introduced to treat neurological illness. Previous studies have stated that the bioactive compounds of *Cullen corylifolium* such as bavachinin, bavachalcone. bavachin and isobavachalcone, contrastingly suppressed the neuroinflammation, key AD-related protein targets, oxidative damage like glycogen synthase kinase 3 beta and acetlycholinesterase in vivo [33].

Simultaneously, isobavachalcone has been reported to be an effective treatment for Parkinson's disease that is caused by the MPTP , extends mice's stay on the Rota rod and reduces their neural Necrosis [34]. Isobavachalcone also reduces production of the IL-6 and the IL-1 beta in the PD mice brain and thus blocked the activation of microglia [34]. Additionally, neobavaisoflavone also showed a great inhibitory impact on the H2O2 -driven cell demise in hippocampal cells(HT22) and in vitro, isobavachalcone significantly lowered the activation of BV-2 microglia and generation of the NO by LPS [34].Also bavachinin (pan-PPAR agonist), was discovered to be a activator that activates the all three isoforms of PPAR [34]. Suggesting that flavonoids may have

a significant neuroprotective effect. Various studies revealed that Nrf2 mediated neuroprotective impact of active ingredients of *Cullen corylifolium* on cerebral ischemia-reperfusion injury, Parkinson's disease [35], Alzeimer's disease [36] and Vascular dementia [37]. Nrf2 (endogeneous) is the primary controller of the anti-oxidant response and a sign of oxidative stress. According to in vitro and in vivo research, isovavachalcone might function as a possible neuroprotective medicine by enhancing Nrf2 expression and activity ,when it comes to treating diseases: Alzeimer's disease [38], Parkinson's disease [39],cerebral ischemia-reperfusion injury, Vascular dementia [37] and cerebral ischemia-reperfusion injury [40]. The medicinal potential of the bavachalcone and other flavonoids in the Chinese Herbal Medicine for the illnesses of brain were enhanced by the upregulation of EPO's expression, which plays a neuroprotective function(Figure 6).

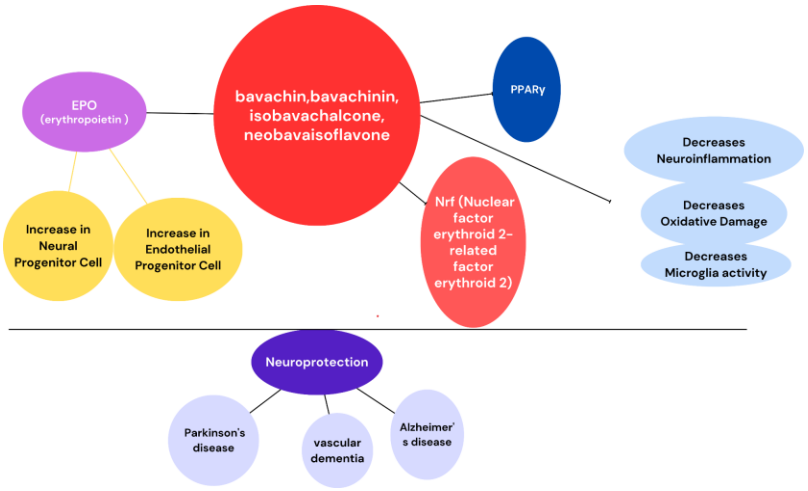

Figure 6:The schematic representation of how various flavonoids promote EPO , Nrf2, PPARγ recruitment and also handles anti-inflammatory activities to have neuroprotective benefits.

CONCLUSION

In conclusion, the review paper summarises the medicative effects of *Cullen corylifolium* seeds with biocompounds (bavachinin, bavachin, bavachalcone, isobavachalcone, and neobavaisoflavone) on ageing -related diseases like Cardiovascular diseases, Diabetes, Neurological diseases(such as PD, AD and VD) and osteoporosis .The age-related diseases are induced by various biochemical and genetic pathways associated with longevity.This paper also reviews the effects of these bioactive compounds of bakuchi on various pathways such as HIF-1 alpha, AMPK, MnSOD, Nrf2, PGC-1 alpha ,Wnt signaling pathway and others.

The discussion of the medicative effects of the *C.corylifolium* seeds will help to diagnose and improve the treatment of various age related disorders leading to the development of potential intervention of age- related illnesses.

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