

The Counteracting Performance of Phytoconstituents Against Neurodegeneration Involved in Parkinson's Disease

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Abstract: Parkinson's disease (PD) is age associated neurodegenerative disorder of the central nervous system. The PD is marked by selective degeneration of dopamine neuron in the specific part of brain called substantia nigra which leads to several motor and non-motor symptoms. The cause of diseases rests uncertain, however the factors like oxidative stress, aggregation of alpha-synuclein protein, mitochondrial dysfunction, neuro-inflammation and many others contribute in development of Parkinson's disease. The current available pharmaco-therapeutics, focused on replenishing the striatal dopamine level but none of them able to halt disease progression. The existing treatment is hindered by the definite boundaries such as it fails to cure disease, provide only symptomatic relief, safety issues and cost of treatment is also more. As the existing treatments are hindered by therapeutic restrictions and with certain adversarial effects; thus, there is a requirement to improve fresh in addition other operative medications with less adversarial effects. The purpose of present manuscript is to explore the capability of phytoconstituents with neuroprotective assets counter to neurodegeneration concerned in PD and encourage expansion of future novel management approaches supported by natural sources.

Index Terms: Parkinson's disease, neurodegeneration, phytoconstituents, Natural products neuroprotective, signaling pathways

I. INTRODUCTION

Parkinson's disease (PD) is age associated neurodegenerative disorder (M. Myhring et al., 2012) marked by loss of dopamine

neurotransmitters in part of midbrain called substantia nigra which will affect physical, physiological social and functional status of an individual's (Goodwin et al., 2008). PD was 1st defined in 1817 via Dr. James Parkinson's which he called as "Shaking Palsy" (Lance et al., 1963). Parkinson's disease shows sure motor symptoms like tremors, muscle weakness and non-motor symptoms such as (William Dauer & Serge Przedborski, 2003) neuropsychiatric manifestations, sleep conflicts, and gastrointestinal upset (Chaudhuri & Schapira, 2009). It is reported that around 6.3 million individuals hurt from PD worldwide. The highest incidence of PD is found in China which is more than 1.7 million people, while lowest incidence occurs in India (Bala & Gupta, 2013). The exact root of PD is still not known but there are several factors which are responsible for development of PD. The occurrence of Parkinson's disease is due to mechanisms such as oxidative stress, mitochondrial respiratory chain dysfunction, ubiquitin proteasome system dysfunction proteolysis defects, inflammation to neurons, deactivation dopamine transporter (DAT, abnormal deposition of a-synuclein and cell apoptosis (Moore et al., 2005). Environmental influences like exposure of rotenone and MPTP causes ROS generation via mitochondrial dysfunction which leads to disturbance in certain cellular pathways involved in neuronal degeneration (Kiebertz & Wunderle, 2013). The hallmark of PD is lewy body formation (Antony et al., 2013).

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The main component of Lewy body is protein called alpha synuclein which responsible for in axonal transport, function synaptic vesicle and neuronal plasticity (Cheng et al., 2011). The factors like genetic mutation, oxidative and nitrosative stress mitochondrial dysfunction leads to aggregations and misfolding of synuclein protein. Abnormally aggregated protein may lead to formation of lewy bodies which will inhibit normal cellular function such as axonal transport and protein turnover via ubiquitin proteosomal or chaperone mediated autophagic system (Stefanis, 2012). The alpha synuclein in LBs further leads to autophagy, vesicular homeostasis and neuroinflammation and mitochondrial dysfunction and thus the neurodegeneration ((Wong & Krainc, 2017). Several molecular and cellular paths show vital role in neurodegeneration and so they do in Parkinson's and molecular pathways are mainly being focused and studied to evolve new drugs to ameliorate the disease. A few molecular pathways involved in PD have been studied (Sainani et al., 2020)(Desai et al., 2020).

The current therapy available for management of PD includes numerous medicaments, like L-DOPA, MAO-B inhibitors, COMT-Inhibitor and DA agonists, which increases the dopamine production and activities in the brain (Oertel, 2017). Although from many years L- dopa use for management of said disease yet incessant treatment with L-dopa causes dyskinesia and motor fluctuation (Tronci & Francardo, 2018). The other pharmacological treatments have certain adverse effects like confusion, hallucination, hepatotoxicity and the available pharmacological treatment only provides symptomatic relief and none of them able to cure PD. When pharmacological interventions fail to manage PD, surgical treatment is recommended. Deep Brain Stimulation and globus pallidus internus (GPI) is presently the best surgical technique for management of PD, and specifically improves motor instabilities and uncontrolled involuntary movements in advanced PD. Lesion surgeries are also used which includes thalamotomy, pallidotomy, subthalamotomy etc; but their application is much less in the present time since of the hazards connected with a surgical lesion procedure. The current available treatment is hampered by certain limitations, such as, it fails to cure disease, provide only symptomatic relief, safety issues, and high cost of treatment. As discussed earlier the current pharmacotherapeutics approach having some restrictions and also certain adverse effects hence there is strong need to find out alternative option with more usefulness and minor adversarial effects for treatment of PD. As Nature had provided many molecules to cure various diseases, the intention of current manuscript is to deliberate the natural molecules which having strong neuroprotective potential in contradiction of different neurodegenerative pathways tangled in PD and to encourage the expansion of upcoming novel treatment stratagems based on natural sources(Fox et al., 2018; Krack et al., 2017)

II. NATURAL PRODUCTS USED IN PARKINSON'S DISEASE THERAPEUTICS:

Currently, many societies prefer herbal nutraceuticals for their prime healthcare. Almost More than half of the marketed formulations are obtained from nature.. In the last few years, many researchers have investigated potential uses of various natural products and herbs for treatment of PD. Some herbs have demonstrated to have more effectiveness, more reliability when compared to the available therapeutic strategies the usual synthetic drugs(M.J. & A.D., 2005; R Desai et al., 2019).

A. *Baicalein*:

Baicalein is type of flavonoid originally found in plant of *Scutellaria lateriflora*(Sithranga Boopathy & Kathiresan, 2010). Baicalein shows manifold activities counting antioxidant, antiviral, anti-inflammatory, and is also used against cardiovascular illness (W. H. Huang et al., 2006). The ethanolic extract of *Scutellaria baicalensis* decreases activity of COX-2 and iNOS protein and thus decreased levels of nitric oxide (NO), COX-2, and PGE2 neuroinflammation formation and prevents the generation of ROS, ATP depletion, apoptosis, membrane mitochondria membrane disruption,etc (Jeong K, n.d.; X. X. Li et al., 2012).Baicalein decreases mitochondrial reactive oxygen species production, shows improvements on membrane integrity level, increased Bcl-2/Bax fraction, and decrease cytochrome C release and thus promote active mitochondrial respiration (He et al., 2009). Baicalein exerts neuroprotective effects by Tyrosin hydroxylase level in brain (Mu et al., 2009). ROS Scavenging activity of baicalein is due to its complex structural similarities with catechol (Mandel & Youdim, 2004). Baicalein exerted neuroprotective effect by upregulation of DA and 5-HT, it also inhibit oxidation and the inflammatory responses neuronal cells(Mu et al., 2011).The adjacent dihydroxyphenyl molecule of *Baicalein* combine then obstruct accumulation of α -synuclein in SH-SY5Y(Lu et al., 2011). It is reported that baicalein up-regulated AKT protein phosphorylation thus baicalein prohibited oxidative damage by stimulating PI3K/AKT signaling pathway (Z. Zhang et al., 2012). These outcomes propose that baicalein has powerful neuroprotective action and could stand as potential therapeutic agent in PD.

B. *Curcumin*:

Curcumin, des-methoxycurcumin and bis-desmethoxycurcumin arte the active chemical constituents of *Curcuma longa*(Marchiani et al., 2013). The other two curcuminoids. *Curcuma longa* was proved to have anti-apoptic, anti-oxidant, antiparasitic,and neuroprotective effects. These effects are due to its active polyphenolic fraction of *curcumin* (S. C. Gupta et al., 2012; Maheshwari et al., 2006).*Curcumin* decreases α -synuclein accumulation tempted cellular toxicity. cytoprotective activity is

due to inhibition caspase-3 activation which is a pro-apoptotic enzyme, inactivation of which may leads to inhibition of apoptosis process (M. S. Wang et al., 2010). Curcumin shows inhibitory action on abnormalities in structure of alpha-synuclein thus halts lewy body formation, it might be due to its capability to scavenge ROS, and inhibitory action on caspase dependent and caspase independent apoptotic pathways of cell death (Liu et al., 2011; Pal et al., 2011). Curcumin thus, enhances α -synuclein, and synphilin-1 solubility make them non-toxic (Pandey et al., 2008). Curcumin preserves dopaminergic neurons by its strong antioxidant, antiinflammatory and ability to restores mitochondrial dysfunction, suppression of AChE action, etc (Khatri D.K. & Juvekar A.R. 2016). Curcumin is not only having ROS Scavenging ability but it also helps in up regulation of endogenous antioxidants. (Ji & Shen, 2014). The brain iron content is increased in PD (Jiang et al., 2017) which results in origination of hydroxyl ions, causes self oxidation of DA which further forms H_2O_2 radicals (Ben-Shachar et al., 1995). Curcumin induces activation of regulatory proteins which is involved in iron metabolism and a reduction in levels of such proteins responsible for systemic regulation of iron i.e. hepcidin thus regulate brain iron level (Jiao et al., 2009). Curcumin initiates nuclear translocation of TFEB by binding with its n-terminal residue. By activating TFEB, curcumin activated autophagy-lysosomal pathways. (Song et al., 2016). Phosphorylation of JNKs releases cytochrome C leading to mitochondrial dysfunction. Thus, inhibition of the hyperphosphorylation of JNKs by curcumin prevents the mitochondrial dysfunction and nerve cell damage (Pan et al., 2012).

C. Milk thistle:

The botanical name for milk thistle is *Silybum marianum* plant family Asteraceae. Silymarin flavonolignans is obtained from the seeds of *Silybum marianum* containing silybinin, isosilybinin, silydianin, silychristin and the dihydroflavonol of taxifolin (Radjabian et al., 2008). The cytoprotective, free radicle scavenging ability, and neuron-protective potential against inflammatory mediators of silymarin has already proved. Silymarin increases dopamine and serotonin levels in dose dependent manner. Silymarin upregulate the catecholamine neurotransmitters level by inhibiting monoamine oxidase-B and thus averts transformation of DA to DOPAC (Pérez-H et al., 2014). Silymarin avoids the development of amyloid- β (Ab) aggregates and fibrils β (52) and averts Ab-mediated neuroinflammation by hindering inflammatory agents such as NF- κ B, TNF etc. further due to inhibition of neuroinflammation it also regulates neuronal count by upregulating levels of trophic factors and downregulating apoptotic pathways (C. Wang et al., 2012; Y.-C. et al., 2010). In addition to that activation of Estrogen receptor-b (ER-b) leads to neuroprotection. Silymarin having

affinity towards this receptors, silymarin binds with ER-b receptors and exerts neuroprotection (Seidlová-Wuttke et al., 2003).

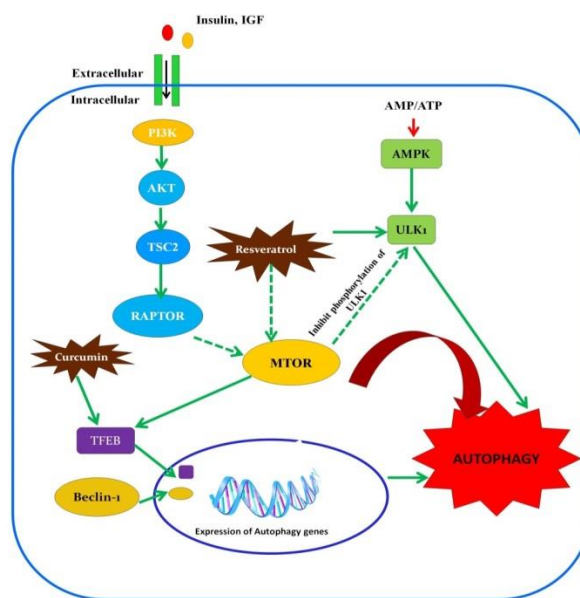


Fig 1. Relationship between curcumin and resveratrol with autophagy lysosomal pathway.

D. Resveratrol:

Resveratrol is polyphenol obtained from isolated from *Polygonum cuspidatum* plant, widely found in grape products, for example wine and peanuts (Baur & Sinclair, 2006; Bradamante et al., 2004). Resveratrol has antioxidant, atherosclerosis, carcinogenesis, neuroprotective activities (Bhat et al., 2001). Resveratrol reduces α -synuclein aggregation via autophagy induction pathway leads to death of abnormally aggregated proteins (Wu et al., 2011). A treatment with resveratrol reduced apoptosis in MPP+ intoxicated PC12 cells. The reticence of apoptotic cell death is governed by its ability to impede cytochrome C and nuclear translocation of the apoptosis-inducing factors (Bournival et al., 2009). However, it has been found that silent information regulator two proteins (SIRT1) is an enzyme deacetylates proteins that contribute to cellular regulation and plays a crucial role in neuroprotection (Pallas et al., 2009; Sinclair & Guarente, 2006). Resveratrol activates SIRT1 that leads to deacetylation of PGC-1 α , a protein and thus neuroprotection.

Peroxisome proliferator-activated receptor- γ (PPAR- γ), is a protein which acts as a novel target for neurodegenerative disorders. Activation of PPAR- γ increases expression of anti-apoptosis proteins like Bcl-2 and thus prevents apoptosis and mitochondrial damage. (Dasgupta & Milbrandt, 2007; Fuenzalida et al., 2007) Resveratrol also inhibit neuroinflammation by inhibition of microglia so on alteration of expression of inflammatory mediators like COX-2 and (TNF α) in the SNPC

(Khan et al., 2010; Q. Zhang et al., 2015).

E. *Bacopa monniera*:

Bacosides is major chemical constituent of *Bacopa monniera* belonging to family *Scrophulariaceae*. The major phytoconstituents of *Bacopa* include bacosaponin, monnierasides I- III, plantainoside B, cucurbitacin, etc (Ohta et al., 2016; Vishnupriya & Padma, 2017). Bacoside A is the most potent constituent of *Bacopa*, which is composed of bacoside A3, bacosaponin C, bacoside II, and bacoside X (Deepak M et al., 2013). *BM* is used in treatment of alzheimers, schizophrenia, and has anti-parkinsonian, antistroke, anticonvulsant potentials (Mathur et al., 2016). The anti-parkinson effect of *Bacopa* is evaluated by Siddique et al. in *Drosophila* fly their findings propose that, *Bacopa* improves neuronal survival by obstructing oxidation of cells, and improving functional capacity i.e. behavioural abnormalities. (Siddique et al., 2014). *Bacopa* extract shows improvement in motor and cognitive function by upregulating expression of TH in SNpc (B. Singh, Pandey, Verma, Ansari, et al., 2016; M. Singh et al., 2012). Administration of *Bacopa* shows positive potentiometric effect on mitochondrial membrane potentials and its complexes specifically regulate complex I in order to impede ROS activated apoptosis mediated neuronal cell death against Paraquat and MPTP induced SK-N-SH human neuroblastoma cell lines (Hosamani & Muralidhara, 2010; Shobana et al., 2012). Consequently, *Bacopa* could be a potential anti-parkinsons herbal drug.

F. *Gastrodin*:

Gastrodia elata (GE) is a saprophytic perennial herb, belonging to the family of *Orchidaceae*. The major chemical constituents are *gastrodin*, vanillyl alcohol, 4-hydroxybenzaldehyde, and vanillin (Taguchi et al., 1981). GE is effectively used as an anticonvulsant, analgesic and sedative in vertigo, general paralysis, and epilepsy and also shows antioxidant, antiasthmatic, antimicrobial, and anti-mutagenic activities (Jang et al., 2010; Ojemann et al., 2006). GE extracts have a neuronal protective action due to the presence of Amyloid β -peptide, and the protection was associated with increased dopamine concentration and decreased dopamine turnover in striatum (Kumar et al., 2013). Administration of *gastrodin* extract successfully progresses dopaminergic cell viability as well as obstructs cytotoxicity. The neuroprotective activity might be due to its ability to down regulate the elevated ROS levels, reduction in Bax/Bcl2 ratio and subsequent proteolysis of poly (ADP-ribose) polymerase (PARP). (Kim et al., 2011). *Gastrodin* also shows neuroprotective effects in the subchronic MPTP induced mouse model of PD due to its anti-apoptotic and antioxidant activity, further it also shows improvement in motor impairment when evaluated in the pole and rotarod tests respectively.

Vanillyl alcohol confirm anti-inflammatory activity by tremendous reduction in levels of inflammatory and pro-inflammatory mediators including cytokines, TNF- α , and IL-1 β by means of hindering the NF- κ B signaling pathway and phosphorylation of MAPKs pathway (Dai et al., 2011). Overall outcomes specify therapeutic utility of *gastrodin* in PD and could be an emerging therapeutic tool in PD therapeutics.

G. *Mucuna pruriens*

Mucuna pruriens (MP) also known as 'atmagupta', 'cowhage' or belonging to the family *leguminosae* (Kavitha & Thangamani, 2014). MP contains non-protein amino acid 3-(3,4-dihydroxyphenyl)-L-alanine (L- DOPA). It also contains glutathione, gallic acid, and beta-sitosterol (Eze et al., 2017). MP displays various activities like anti-microbial, anti-inflammatory, antioxidants and neuroprotection. (Chaudhari et al., 2017). The behavioural, motor and cognitive abnormalities are well rescued by MP via upregulation of dopamine. MP also facilitated neuroprotection by dropping levels of apoptotic proteins and increasing intensities of the anti-apoptotic proteins separately (Yadav Sk et al., 2016). MP seed extract improves mitochondrial and synaptic functions and plays crucial role in neuronal survival and improve TH expression in *Drosophila* and mouse model of PD (Maheshwari et al., 2006; Yadav et al., 2013). MP has substantiated claims on its efficacy and safety in PD and there are indications that it is more effective than the synthetic levodopa in reducing dyskinesia (Pal et al., 2011; B. Singh, Pandey, Verma, Singh, et al., 2016).

H. *Pueraria lobata*:

Pueraria lobata (PL) is a Chinese herb of Leguminosae family plant traditionally used for management of diseases like antipyretic, antidiarrhetic, active against angina pectoris, hypertension (Sun et al., 2008; Woo et al., 2013). Anti-PD outcome of PL is due to its capacity to upregulate DA and TH favorable neuronal expressions alongside upregulation of neuronal surviving trophic factors like GDNF (Zhu et al., 2010). *Pueraria* contains active components daidzein and genistein, which impedes caspase dependent apoptosis and thus improves cell viability (Lin et al., 2010). Further mechanistic Investigation Demonstrated that Puerarin inhibits caspase-3 enzyme and nuclear translocation of apoptotic proteins like p53 and Bax (Zhu et al., 2012). The gene *DJI* plays an important role in antioxidant mechanism, synaptic plasticity. PL exerts antioxidant activity by positive expression of *DJI* and *SOD* thus reduce neuronal loss (R. Li et al., 2013). Some of the studies discovered the mechanistic approaches behind antiparkinsons activity via anti-apoptotic potential of PL is downregulation of CYT C, increase production of phosphor-akt, upregulation of mitochondrial membrane potential consequently inhibit H₂O₂ mediated apoptosis ruled by pi3k/akt signalling (Bo et al., 2005).

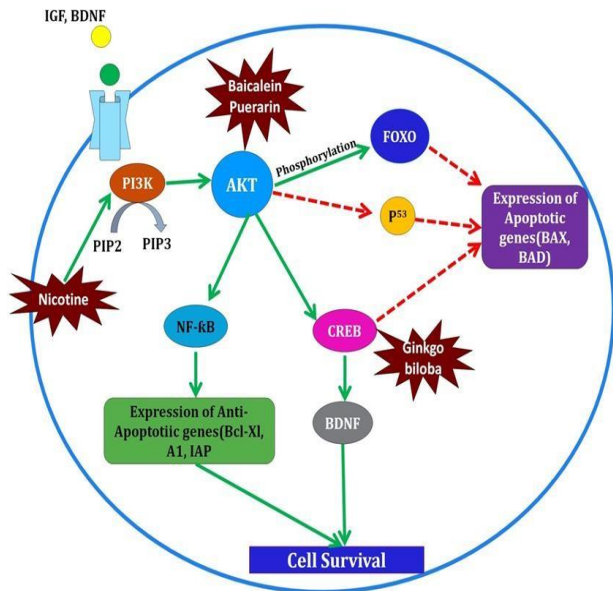


Fig 2. Effect of Baicalein, Puerarin, Nicotine, and Ginkgo on different signalling pathways involved in Survival.

I. *Ginkgo biloba*

Ginkgolides and Bilobalide are the prominent active constituent of ginkgo biloba plant of family ginkgoaceae (Beek, 2002; Smith et al., 1996). GB shows strong antioxidant, antianxiety, antitumor, antimicrobial and neuroprotective activities (Chan et al., 2007). The GBE treatment improves locomotor activity, superoxide dismutase and glutathione also improved the manifestation of TH and DAT (Kuang et al., 2018). GBE inhibits caspase dependent and independent neuronal apoptosis which is mediated by downregulation of intracellular calcium ions mediated by regulation of calbindin D28K mRNA and thus results ion neuroprotection. (Meng et al., 2007). Supplementation with ginkgo biloba causes phosphorylation of transcriptional factor CREB which turn into up regulation of trophic factors like BDNF, GDNF, ETC. It also improves antioxidant status, all together responsible for improvement in cognitive and motor dysfunction. (Belviranli & Okudan, 2015). GBE exerts anti-neuroinflammatory action in LPS- induced mice model. Anti-neuroinflammatory activity of Ginkgo biloba is due to its ability to hinder the discharge of pro-inflammatory cytokines and the stimulation of MAPKs signalling (J. Ye et al., 2019). Further study shows that neuroprotective effects of Gbe is because of its positive action on Akt signalling which leads to anti-apoptotic activity (Yu et al., 2018)

J. *Withania somnifera* :

Withanolides, withanine, somniferine, somnine, somniferinine, withananine, pseudo-withanine, are the chief constituents obtain from *Withania somnifera* (Ws), belonging to family *Solanaceae* (Dafni & Yaniv, 1994; Kulkarni & Dhir, 2008). WS also

upregulates endogenous antioxidants enzymes like GSH and GPx and also attenuates inflammatory responses (Bhatnagar et al., 2017; Sankar et al., 2007; G. Singh et al., 2010). WS significantly improves behavioural and cognitive functions with upregulation of DA levels in SNpc (RajaSankar et al., 2009) together with it also alleviate neurotoxins tempted mitochondrial dysfunction and neurotoxicity in the *Drosophila* (Manjunath & Muralidhara, 2015). The neuroprotective effect of *Withania* is mainly due to its ability to increase DA and TH levels and antioxidant potential (Prakash et al., 2013).

K. *Ginseng*:

Ginseng consists of Ginsenosides as major phytoconstituent which mainly contributes in neuroprotective, anti-inflammatory, antioxidant activities (K. T. Choi, 2008). It has been reported that panax ginseng attenuates apoptosis by increasing levels of anti-apoptotic proteins and by diminishing levels of apoptosis inducing factors such as like Bax, Bcl-2, and cytochrome c thus guards dopaminergic neurons from oxidative stress (X. C. Chen et al., 2003, 2005; S. Hu et al., 2011). Overexpression of Cyclin dependent kinase (Cdk5) shows a vital part in occurrence of PD. Normally, p35 phosphorylated Cdk5, which upkeep neuronal existence (Cheung & Ip, 2012). However, Ginsenoside Rg1 attenuates MPTP mediated over activation of Cdk5 thus prevent neurodegeneration (over activation of Cdk5 causes increase in p25 level and downregulation of p35, therefore loss of neurons) (Jun et al., 2015; Kanungo et al., 2009). Korean red ginseng shows antioxidant effect by activating Nrf2 transcriptional factor, alleviates neuroinflammation by suppressing NF-KB pathway (J. H. Choi et al., 2018) and hindering activation of microglia and astrocytes thus diminished the discharge inflammatory mediators in the SNpc (Heng et al., 2016). Additionally, ginseng shows neuroprotective properties in PD thru Wnt/ β -catenin signalling and could consequently deliver a novel tactic for the management of PD (T. Zhou et al., 2016). Overall Ginseng shows its neuroprotective effect by its antioxidant, anti-inflammatory, anti-apoptotic mechanisms.

L. *Nicotine*:

Nicotine is obtained from *solanaceae* family plants (Andersson et al., 2003). The reduction intracellular calcium ions play a crucial role in almost all apoptosis pathways in addition to that calcium also has significant importance in regulation of levels of neurotrophic factors and excitability of neurons. Nicotine significantly decline intracellular calcium ion levels in neurons subsequently several cell apoptosis signaling are constrained, neuronal fieriness is improved, and neurotrophic factors are triggered thus neuroprotection, (Mudo et al., 2007; Quik M et al., n.d.). The neuroprotective effect of nicotine is governed by activation of 7 nicotinic acetylcholine receptor ($\alpha 7$ -nAChRs), stimulation of this receptors initiated several processes like upregulation of trophic factors (GDNF), inhibition of lewy body

formation, attenuation of microglia and thus neuroinflammation and also stimulate expression of synaptic proteins tangled in neuronal survival which all together reflects as improvement in motor and cognitive functional capacities(Hong et al., 2009; McKay et al., 2007). Further studies suggest that activation of $\alpha 7$ -nAChRs is mediated through Wnt/ β -catenin (Y. et al., 2017)PI3K/Akt cellular pathways (Kardani et al., 2017; Y. et al., 2017).

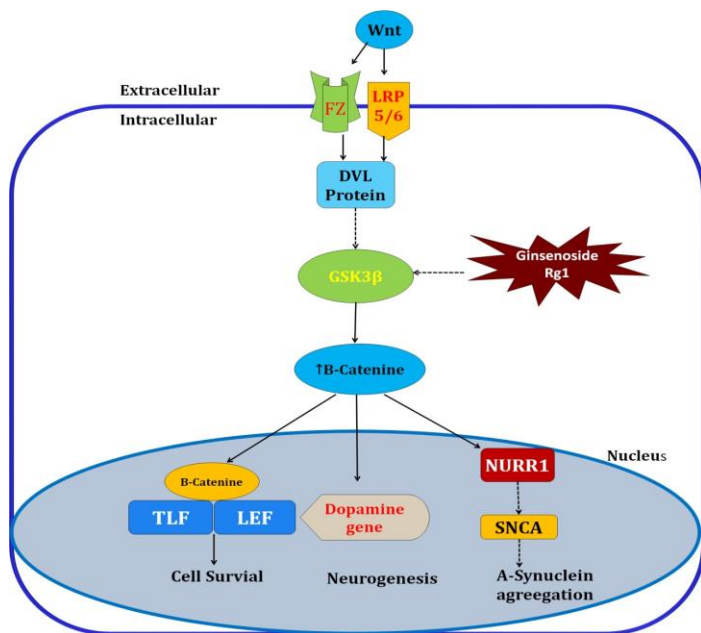


Fig 3. The association concerning Ginsenoside Rg1 and wnt/ β -catenine signalling pathway.

M. Magnolol:

It is isolated from plant *Magnolia officinalis* family *Magnoliaceae* (Rempel et al., 2013). The TLR4 Receptors turn into the reinvigorating of NFKB-MAPK signalling which further subjected to release inflammatory mediators including cytokines, magnolol inhibit expression TLR4 receptors thus prevent lipopolysaccharide induced neuroinflammation (Fu et al., 2013). Magnolol shows strong antioxidant activity is result of its capability to upregulate endogenous antioxidant enzymes (Muroyama A et al., 2012). The neuroprotective properties and its capability to downregulate signaling mechanisms (P38/MAPK) is tangled in neurodegeneration(J. H. Chen et al., 2014). Another active constituent of magnolia officinalis namely honokiol increases DA levels in SNpc and thus shows significant improvement in motor symptoms like tremors and bradykinesia in animals(H. H. Chen et al., 2018). Magnolol upregulated neuronal cell survival in neurodegeneration mediated by acrolin model, this mechanism governed by regulation of JNK/mitochondria/caspase, PI3K/MEK/ERK, and PI3K/Akt/FoxO1 signaling. In addition, the anti-PD potential of this herb is mainly because of its strong antioxidant capacity and ability to restores levels of DA transporters and TH(Dong et al.,

2013).

N. Green Tea Polyphenols:

The Green tea is obtained from plant *Camellia sinensis* belonging to the family *Theaceae* consisting epigallocatechin-3-gallate (EGCG) as abundant catechin (Chu & Juneja, 1997). The phosphorylation of I κ B leads to nuclear translocation of NF- κ B is vital incidence eliciting inflammatory progressions in the brain. EGCG inhibit phosphorylation of I κ B and thus decreases the TNF- α , nitrite level and increases the levels of dopamine(AL-amri et al., 2013; Virmani et al., 2013).Specifically, dopaminergic neuronal defense employed by EGCG possibly because of the stimulation of MTOR, PI-3kinase-Akt pathways (Ramassamy, 2006). Green tea polyphenols having strong antioxidant, iron chelating potential and that results in prevention of accumulation of iron and α -Synuclein (α -Syn) abnormalities(Ascherio,Zhang, 2011 C.E.). Green Tea inhibit the fibrillogenesis and thereafter it converts bulky and developed α -synuclein and $\alpha\beta$ fibrils into simple and reduced protein structures thus building them less toxic (JC, 2012). Antioxidant activity might occur through sirt1/pgc-1 α signaling(Q. Ye et al., 2012). EGCG possibly will significantly improves neurobehaviorals symptoms and decrease neuronal apoptosis and α -synuclein expression in SNpc of rats with PD. EGCG may improve the consequence of Parkinson, and the mechanism connected to the stimulation of AKT/GSK-3 β /mTOR pathways(W. Zhou et al., 2019)

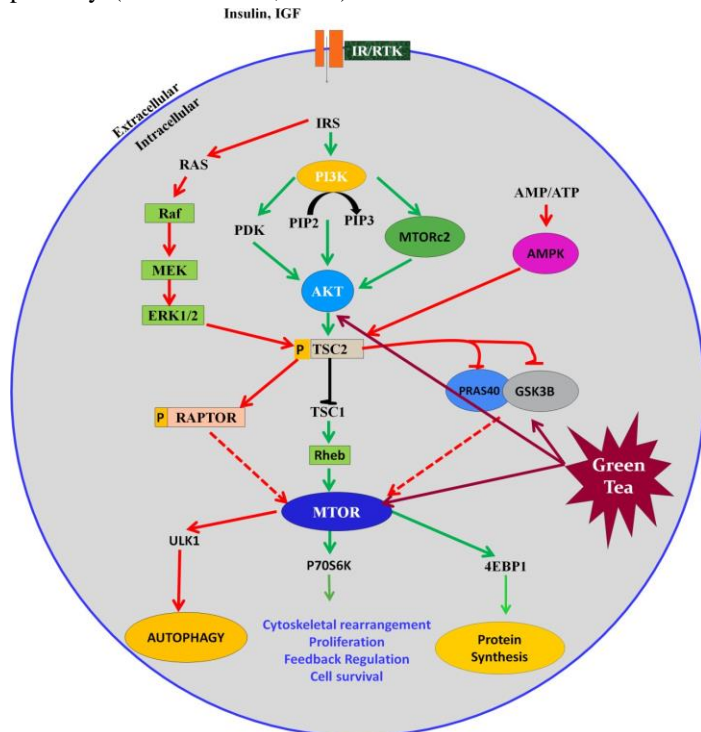


Fig4. Effect of Green Tea polyphenols on different Signaling Pathways involved in cell survival.

O. Triptolide:

Triptolide, is obtained from roots plant *Tripterygium wilfordii* belonging to the family *Celastraceae* (R. Gupta & Sharma, 2006). It has been found that triptolide defends dopaminergic neurons in LPS induced neuroinflammation model by inactivation of microglial cells and thus prevents the release of inflammatory and pro-inflammatory mediators including cytokines (H. F. Zhou et al., 2005). Additional study demonstrated that the inhibition of microglia and astrocytes activation is due to up-regulation of metabotropic glutamate receptor 5 which acts via activation of MAPK signaling pathway (Y. Y. Huang et al., 2018) Triptolide suppress inflammation by inhibiting prostaglandin E2 (PGE2) production, which is a potential possible mechanism of anti-inflammation. Triptolide positively regulate JNK phosphorylation (COX-2) appearance and PGE2 formation in lipopolysaccharide treated microglial cell cultures (Gong et al., 2008) Triptolide up-regulate the production of auto phagosomes by upregulating expression of LC3-II protein which leads to the formation and accumulation of GFP- LC3-II which results in initiation of autophagy pathway (G. Hu et al., 2017)

CONCLUSION

The most common neurodegenerative disorder, Parkinson, does not have any remedy that can actually antagonize the cause of the degeneration that persists. Another fact that should be paid attention is that there are multiple pathways which together contribute to the death of the neurons. Hence it is obvious that a complete therapy should include multiple molecules that can antagonize every degenerating cause to ultimately stop neuronal death and fight the disease. Therefore, one such complete therapy can be achieved by focusing on the structure of therapeutic molecules to extract out their essential moiety which is responsible for binding and antagonizing the killing molecules like ROS, NO, protein aggregates and so on. The aim of the current review was to extract out different natural substances that can serve anti-PD activity with a special emphasis on their structural activity to explain their mechanism of action at the molecular level.

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