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Neuropharmacological Consequences of Variant Drugs

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ABSTRACT

Neuropharmacological effects deals with the influence of drugs on nervous system which harvest the changes in mood, behavioral action of an individual. The drugs are characterized by the chemical substances that communicate with the neurons which have different impacts on nervous system. It may either conducts the abusive or pleasure response which depends on the neural chemicals activity and concerns with the licit and illicit drugs. The elucidation of drugs via LC/MS shows its exertion on the brain components. The computational model helps in the identification of signaling pathways that trigger or inhibit the neurotransmitters. The licit drugs have indisputable responses on CNS. It imparts neuroprotection by either stimulating or inhibiting the receptor, by down regulation yield anti-nociceptors. However, the illicit drugs have negative acknowledgment on the body as in nicotine the fewer amounts provides benefits but in higher amount mimics the activity of brain receptors and replaces it. Many other drugs induce neurodegenerative disorders. Due to advances in field of neuropharmacology innumerable drugs are available for feasible treatment. The main objective of this review is neuropharmacological consequences in correlation to licit and illicit drugs that what type of responses generated by using these drugs, the neurodegenerative disorders, and their restoration via current treatment.

Keywords: Neuropharmacology, Nervous system, Licit, Illicit, Signaling pathways

INTRODUCTION

The neuropharmacology is related to two words. The neuro related to neurons in brain and pharmacology is concerned with study of drugs. Neuropharmacology is the study of neurotransmitters, neuromodulators, and their effect on the brain, most importantly the central nervous system. The history of neuropharmacology is started with just four drugs and now innumerable drugs are approved being available in clinical practices for neurologist. Drugs are the chemical substances that are characterized in four groups. The first group in which drugs acts as pharmacodynamic agent i.e., sedatives, analgesics etc. The second involves the drugs that act on central nervous system i.e., antidepressant, hypnotic drugs etc. The third category includes the drugs that have chemotherapeutic action i.e., sulfonamides, antimicrobial etc. The last groups involved the supplementary agents like vitamins. The chemical structure affects both pharmacodynamics and pharmacokinetics properties of drugs belongs to its subclass 8. Neuropharmacological drugs exhibit different effects on brain. Neurons in the brain communicate with each other via chemical and electrical signals and occur at tiny gaps called as synapses where pre- and post-synaptic neurons comes and exchange chemicals. The presynaptic releases chemical received by post synaptic called as neurotransmitter receptor. Hundreds of neurotransmitters accomplished on brain. The drugs stimulate or suppress the exertion of neurotransmitters and produce potential effect on brain [1]. The world is being globalized enough to promote the usage of neural drugs especially those that imparts bad effects on health and made addictive to it. The study of neuropharmacological variant drugs is focused in order to determine its consequences on brain as well as human health. Some drugs must be approved in the countries that have positive impact and some must be totally banned and restricted throughout the world [2-6].

The drug has been evaluated by LC/MS technique which helps in its identification. For example, the chemical characterization of the extract available as drug obtained from *Calea zacatechichi* by LC/MS reveals the presence of compounds chlorogenic acid, germacranolides, acacetin. It suggests that these compounds have neuropharmacological effects [7]. Computational models of drugs are predicted that adopt the dynamic models and are widely accepted in clinical approaches and neuroscience [8]. The XPPOUT software act as tool for the compassionate of the effect of drug in normal as well as pathological neural mechanisms [9]. The drugs directly effect on the neurons and their excitability is taken place via activation of signaling pathways which either phosphorylate or dephosphorylate the cascade pathways i.e., ions, receptors, channels and produce responses [6]. The drugs used can either be illicit or licit. The licit drugs are that which is not forbidden to practice by law in any country and has beneficial effect on the human health i.e., drugs obtained from *Nigella sativa* [10], *Euphorbia pulcherrima* (EP) [11], *Calotropis gigantea* [12] has positive effects on the CNS. However, the illicit drugs are those that are forbidden to be mobilized by law in most of the countries due to its adverse effects on human health i.e., drugs obtained from *Nicotiana tabacum* [13], *Erythroxylum coca* [14], *Coffea canephora* [15], etc. has pessimistic impact on CNS and ensued in neurodegenerative disorders [16]. Monitoring of therapeutic drugs is very important for proper balancing and maintenance of some FDA approved drugs on Central nervous system. New technologies and herbs has been used in order to develop the novel neuropharmacological variant drugs for the treatment of neurodegenerative disease i.e., particularly Parkinson's disease, stroke, vestibular disorder etc. [17]. The aim of the review is to give understanding of variant drugs in terms of neuropharmacology. It also highlights the characterization and evaluation, development of computational models for the drugs, signaling pathways of neurotransmitters. There is summarization of consequences of both licit and illicit drugs on human health and the medication of neurodegenerative diseases i.e., stroke, Parkinson's disease, vestibular disorders being available.

Variant drugs

Drugs are the substances that produce physiological changes in the body. There are many types of drugs that perform vital functions i.e., anti-depressant, anticonvulsant, analgesic, anxiolytic, memory enhancer [8]. These drugs are based on the physiochemical parameters i.e., lipophilicity, solubility, ionization constant, stability, surface activity, pH, etc. [18]. Drugs are either legal or illegal. The legal drugs term as "licit drugs" are the human rights of health and accessibility to medicine is a matter of concern from few decades. The legal drugs are the few structures that assigned the "Patent Agreements" which may sometime cause difficulties due to expensive medicines [19]. On the other hand, the legal drugs termed as "illicit drugs" are those that are not used under the patent agreements and are abused giving rewarding effects on brain e.g. morphine [20], cocaine [21], heroin [22] etc. The method of illicit drugs is snorting, smoking, skin popping, injecting. The illicit drugs results in number of medical obstacles. As most of illicit drugs are associated with severe infections which are difficult to treat with microbial techniques [23]. Nowadays bad quality or false drugs reached the market through substandard yielding of legitimate medicines and have hazardous effect on health. There should be ban on companies that are availing the substandard drugs. For example, paracetamol are substandard drugs and causes gastrointestinal problems, neuropathies, renal injury and may even cause death [24]. Biological recombinant products brought revolution in modern medicine to treat the disease and fulfill the unmet needs of medical. For example, the development of vaccine, recombinant hemagglutinin for flu. The world is moving ahead by using applying these approaches in medicinal field [25].

Neuropharmacological characterization and evaluation

Nervous system consists of billions of neurons having axons and dendrites, interconnected with each other. There is feed in via axons turn out via dendrites as shown in Figure 1. Neurons have the electrical potential termed as integrators. Drugs as special chemical known as neurotransmitters produces chemical signals through signal transduction pathways are fired on target cell at synaptic cleft at threshold potential like the receptors are target cells in order to produce therapeutic action for which the drug is administrated. Drugs releases either inhibitory or stimulating neurotransmitter as shown in Figure 2. Several drugs have been categorized in order to produce neuropharmacological effects that have medicinal potency on the central nervous system [1]. Some drugs implicit neuroprotective effect, on the other hand some drugs are neurodegenerative.

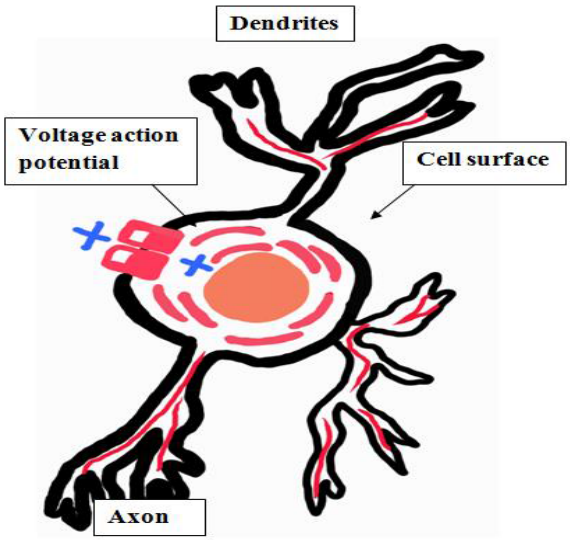

Figure 1 Schematic diagram of neuron depicting dendrites and axons [1]

The characterization and identification of targets remain a fundamental problem among the neurosciences and medicinal chemistry. The emerging techniques in genomics and proteomics promote progress. Neuro active drugs work in nerve cells and effect the activity of electrophysiology [6]. *Calea zacatechichi* is an American plant known as Bitter grass or Dream Herb. It is used in Mexico in order to cure cough, asthma gastrointestinal tract disorders like diarrhea and stomach ache. Moreover, it is used from past decades by traditional rituals for having hallucinogenic activity.

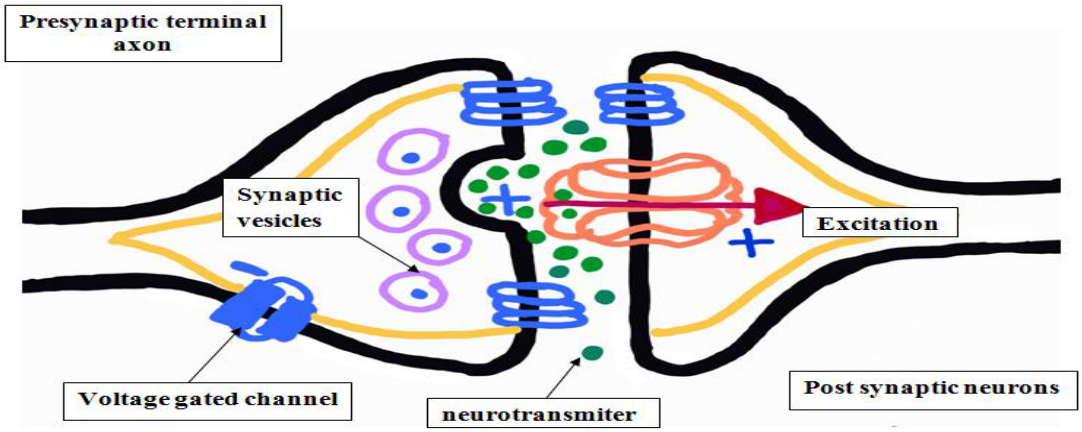

Figure 2 Schematic diagram of postsynaptic and presynaptic neurons releasing neurotransmitters [1]

Evidences from the experiment perform on the mice and their characterization evaluated by LC/MS method. The parameters being measured from aqueous extracts obtained from the *Calea zacatechichi* has no effect on behavior, anxiety, muscular power in the given dosage. However, the chemical characterization reveals the presence of acacetin, germacranolides and chlorogenic acid and their functions in the table a as follows. The *in vivo* results reveal that the neuropharmacological effects are insignificant and lower the pain of abdomen perception. The extracts of *Calea zacatechichi* gives evidences that it can be used to cure medical state due to its antidiarrheal, anti-inflammatory, antimicrobial activities positive effects on human health [7].

Signaling pathways via computational models

The effect of drug on brain activity is stimulated by modulating their influences on the cellular signaling pathways. Synaptic input activated by intracellular molecules by cascades pathways which in turn activate the ionic channels. The

computational models of mathematics depend on biochemical reactions allows prognosis of the drug based changes in the cyclic AMP, Ca^{+2} i.e., second messenger level and modulation of downstream phosphoproteins. The software XPPAUT is designed in order to best suited to solve problems of biochemical kinetics reactions. For example, the computational models for the signaling molecule included in synaptic plasticity which is the neostriatal compartment having spiny projection medium and other in Purkinje cell in cerebella. The software XPPAUT involved following signaling pathways for both models [6]. The computational spiny projection neurons involved the dopaminergic and glutamatergic activation signals pathways which are involved in the generation of cAMP cyclic adenosine monophosphate.

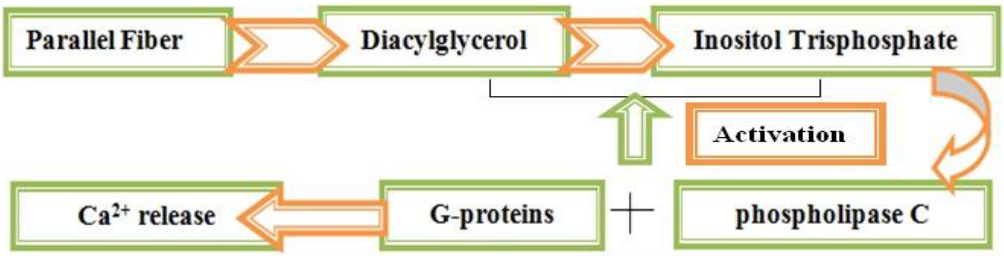

Figure 3 Glutamatergic Signaling pathway of intracellular models involved in plasticity [6]

The first pathway called "Glutamate Pathway" in which there is stimulation to glutamate that elevates the calcium level and follows the pathway as shown in Figure 3.

There is subsequently increase in calmodulin CaM and calmodulin kinase 2 CaMKII. The phosphodiesterase 1B (PDE1B) and protein phosphatase 2B (PP2B). The former one degrades the cyclic AMP. The second one is dopamine pathway involved the activation of PKA protein kinase A via cAMP and adenylate cyclase. Activated protein kinase A increases the DARPP 32 phosphorylation, which inhibits the PP1 protein phosphate. This determines the cAMP dependence on the amount of dopamine the synaptic cleft. As increase in the concentration of dopamine receptors, more will be the modulation of calcium ion in the medium. Either the receptors or amount of dopamine in synaptic cleft increased then the concentration of cAMP directly increased (Figure 4).

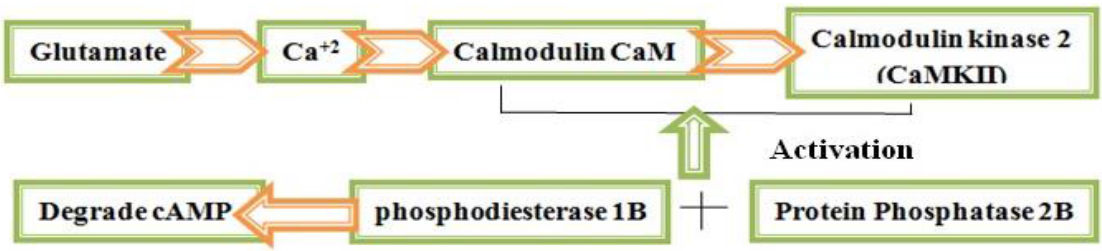

Figure 4 Model of Purkinje cells in first biochemical pathway [6]

On the other hand, when calcium influx elevated then the cAMP indirectly related results in decreasing. The therapies that cause the receptors expression and dopamine release differently effects the cAMP cascades which depends on dose.

The Purkinje cells are present in cerebral cortex of brain. It acts as neurotransmitters that bind to brain receptors and activate or inhibit other neurons. The computational model for Purkinje cell involved three biochemical cascades.

The dendrites of these cells neurons perceive excited inputs via axonal pathways. In the first pathway, Parallel fibers from the cells by receiving inputs activated and subsequently activated the diacylglycerol, inositol triphosphate via G proteins and phospholipase C and results in calcium increase. The second pathway involves the cystic fibrosis stimulation which elevates the calcium level by activating the voltage dependent calcium channels (VDCC) by producing arachidonic acid (AA) [6,26]. The third pathway correlates the DAG, calcium and arachidonic acid elevation and their effect on the active foam of protein kinase C. Overall the Calcium release is modulated by voltage dependent channels [6].

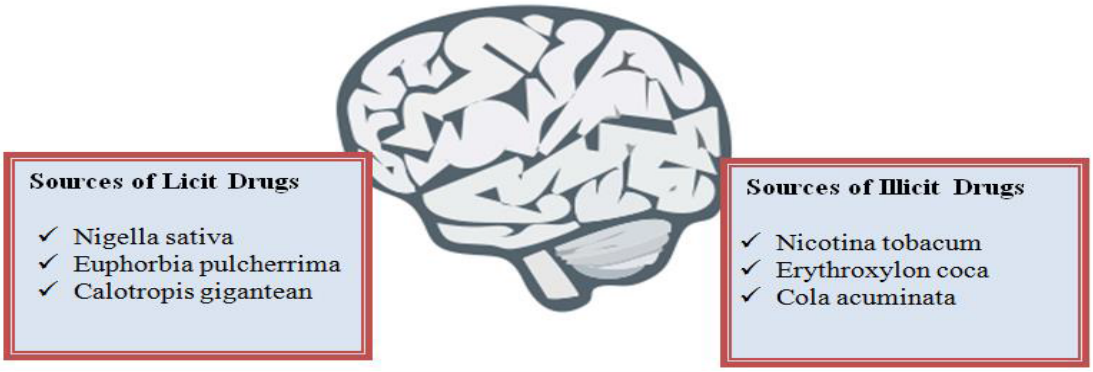

Figure 5 Source of plants containing licit and illicit drugs

Effect of drugs on brain

The neuropharmacological effect on the brain is either by usage of licit or illicit drugs. The sources are shown in Figure 5.

Licit drugs

In case of licit drugs most important being obtained from the plant i.e., is the Nigella sativa considered to be annual plant being used worldwide due to medicinal significance. It is the potent herb against neurodegenerative disease as in multiple sclerosis, Alzheimer disease [27]. However, this herb considered to have anti-convulsant, antidepressant property. The seeds of Nigella sativa composed of essential biomolecules which is carbohydrates, proteins, fibers, a number of vitamins and minerals. The seeds also contain carotene which is converted into vitamin A in later period of development. The active compound is the thymoquinone (TQ) which inhibits the acetyl cholinesterase enzyme and fight again neural disease. It controls anxiety and depression by GABA and nitrite modulations. The TQ increases GABA modulation in unstressed persons having no effect on nitrite level. On the other hand, in stressed persons TQ decreases the GABA level and act as anti-anxiety and antidepressant. Prolong use of drug of Nigella sativa enhances the level of serotonin in the brain and improve the memory and learning experience [27-29].

The *Euphorbia pulcherrima* (EP) plant obtained from *Euphorbiaceae* is also used as drug against skin disease, laxatives, increasing milk production, neurodegenerative disease but have no action on motor coordinated mechanism. It is related to the CNS due to its analgesic and nociceptive property. Pain in the body is induced have two types i.e., central pain and peripheral pain For example the peritoneal injection induces pain in the body, activating the nociceptors by elevating the level of serotonin, histamine, prostaglandins. However, the acetic acid also produces the inflammatory action at the site of pain. *Euphorbia pulcherrima* (EP) drugs administration results in inhibition of increased level of acetic acid and act as antinociception by reacting in both ways either central or peripheral analgesic [30,31].

Calotropis gigantea is a weed that arouse scientist to use it in a positive way. This plant has uncountable medicinal values. Scientist reported the beneficial activity of each part of plant one by one. Flowers are involved in regulation of analgesic activity. Leaves have antibacterial activity that makes this plant more significant. Roots have antimicrobial activity and mainly involved in central nervous system activity. The ethanol extraction from the *Calotropis gigantea* has rugged effect on sedative and hypnotic action. Thiopental drug interact with GABA receptors by neuromodulation allows the entry of chloride ions making channel open for longer passage i.e., up regulate GABAergic activity. On the other hand, decreases the diversion of glutamate receptors, after blocking by thiopental as by down regulate the glutamic activity [32].

Illicit drugs

Illicit drug includes the drugs of abuse having negative impact on human brain as it shows interaction with neurochemical activities of brain. Some of the interactions are related to the properties of the drug. Drugs of abuse have a number of actions on the brain as drugs interact with brain system. One of the most distinguished plants is the *Nicotiana tabacum* as nicotine is the main chemical component. It comes mostly in the foam of tobacco. It can is used

by chewing, smoking, sniffing activity. Scientist perform a number of experiments and come to know that nicotine is the strong agent having effects on central and peripheral nervous system [33,34]. Its small concentration considered to be beneficial but in large amounts nicotine when enters in the body elevates the level of acetylcholine and activate the cholinergic receptors. Regular usage of nicotine makes the permanent changes in the cholinergic receptors of brain and develop tolerance for nicotine as a result make person addict to it. If nicotine level reduces it makes the person crave for it. On the other hand, dopamine also level increases as the nicotine level increases. Nicotine directly do not exceed the dopamine level but through the inhibition of monoamine oxidase A. Regular smokers have high level of dopamine because of reduction of the mono oxidase enzyme that break dopamine [33].

Cocaine is present in the *Erythroxylum coca* plant leaves, which is large herb. The compound is taken from the leaves and then converted into powder, paste or freebase foam via processing. Additional process involves the addition of hydrochloric acid in the paste and converted into powder foam known as cocaine hydrochloride which is administered via snorting. However, freebase is the pure foam of cocaine and produced by separating via chemicals sodium hydroxide or ether and then absorbed easily in the body.

The cocaine in human increases the mood level, alertness, and sense of energy. This would result in the increase attention and concentration, Loss of appetite, reduce fatigue etc. The hazardous effects include the coma, Seizures, delirium, cardiac arrhythmias. The neuropharmacological effect of cocaine is to increase the level of dopamine as causing synapses in brain resulting from the blockage of returning of dopamine in the presynaptic terminal when release from neuron as shown in Figure 6. In the same sense cocaine blocked the serotonin and nor epinephrine reuptake [35].

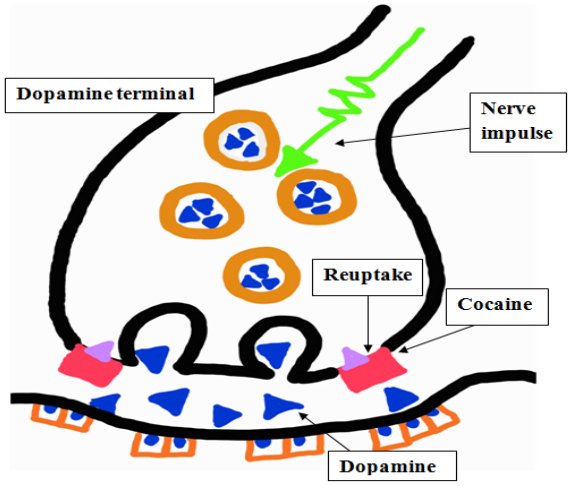

Figure 6 Mechanism of cocaine that blocked the re- uptake of dopamine into terminal presynaptic [5]

Caffeine is the psychoactive substance being widely used in the world may obtained from *Cola acuminata*. It belongs to the compounds methyl xanthine which act as stimulants of CNS. This stimulation of caffeine is due to blockage of inhibition of neurotransmitter "adenosine" receptors. It blocks the adenosine of A1 and A2 receptors. It inhibits the releasing of neurotransmitters as amino acid glutamate. As a result of adenosine blockage, the glutamate activity elevated. Caffeine also elevated the level of serotonin and nor epinephrine which stimulate the CNS. Low doses of caffeine have mild effect however higher doses of caffeine has adverse effects on the CNS [36].

Table 1 Chemical characterization of the *C. zacatechichi* compounds and their effects on human health [7]

Empirical formula	Name	Effects
$C_{16}H_{18}O_9$	Chlorogenic acid	Antinociceptive Effect
$C_{22}H_{28}O_8$	Calein A	Antimicrobial, Anti-oxidative
$C_{21}H_{26}O_8$	Calealactone C	Antimicrobial, Anti-oxidative
$C_{16}H_{12}O_5$	Acacetin	Depressant activity
$C_{27}H_{30}O_{16}$	Rutin	Antidepressant like effect
$C_{27}H_{30}O_{15}$	Rutin without hydroxyl group	Antinociceptive and Antidepressant like effect

Neuropharmacological treatment

There are innumerable brain neurodegenerative disorder occurs due to malfunction in the brain system due to use of mostly illicit drugs. For that purposes neuropharmacological treatment gives positive results on the brain system and help to cure it. The examples in which neuropharmacological treatments use as rehabilitant tool are very vital.

Stroke is one of the major cause of drugs and may lead towards disabilities i.e., ataxia, paralysis, aphasia, paresthesia. The death due to stroke continuously increases as the expectancy towards life increases. Due to socioeconomic burden, there is still deficiency of effective treatments for stroke. Metformin is a drug that has been used for treatment of diabetic patients. Recently, this drug is used for stroke due to its beneficial effects i.e., therapeutic effect in neuro-disorders and reduces the severity of strokes. The metformin act by activate the AMPK, which the regulator of homeostasis, cellular sensor. It is only activated when ATP/AMP levels are elevated which by conformational changes allosterically exposes binding sites for Metformin. Metformin does not directly bind to these sites, however indirectly via respiratory chain inhibition increases ATP/AMP level and activated the AMPK. Further downstream mechanisms activate AMPK and mediate strokes outcomes i.e., AMPK activate other Nuclear factor (erythroid-derived 2)-like 2, or by inhibited the NF-κβ to suppress the neuroinflammation and protect against cerebral ischemia as shown in Figure 7.

Parkinson's syndrome is also one of neurodegenerative disease PD which affects both motor neuro behavioral functions and causes its dysfunction. Treatment for motor dysfunction is well investigated. Levodopa treatment is responsive for mental as well as motor impairments occurring in particular stage of PD. The target of neuropharmacological drugs i.e., cholinergic and catecholaminergic function as remedy of mood, cognitive and psychiatric changes in PD. The other possible treatments for the Parkinson's disease are shown in Table 2.

Table 2 Neuropharmacological treatment of mental dysfunction in PD [2]

Problem	Treatment
Depression	Tricyclics, serotonin reuptake inhibitors, diazepam, ativan
Dementia	Rivastigmine, donepezil, tacrine, galantamine
cognitive deficits	Levodopa
Psychosis	Clozapine, quetiapine, olanzapine, risperidone, rivastigmine, tacrine, galantamine

Vestibular system is highly processing in the regions of the brain and are involved to control many functions i.e., body orientation, posture, visual system etc. The disorder of the vestibular system is because of two effects. The ones of these involves the synapses along with neurons in the vestibular nuclei and releases glutamate and aspartate neurotransmitters whereas these transmitters are send to the many regions of CNS central nervous system and effect it. The available neuropharmacological drugs are as follows as shown in Table 3.

Table 3 List of drugs that effect the neurotransmitter receptors [4]

Drug	Use
Baclofen	Control of Nystagmus (alternating)
Sulpiride	Vestibular sedative
Gabapentin	Control of Nystagmus (Pendular)
Droperidol	Antipsychotic
Dizocilpine	Neuroprotective

The other effect that acts on the voltage gated ion channels as shown in Table 4. Alzheimer's disease is another neurodegenerative disease that disturbs the normal functioning of brain and its structure as well. The accumulations of amyloid beta peptide in the brain having AD compete to amylin in order to bind with amylin receptors of brain.

The current available treatment is the used of exogenous amylin as it is the one of brain hormone. Amylin compete with Aβ and decrease the AD cascade pathways. It provides protective effect as well as improves the learning and memory of individuals [37,38].

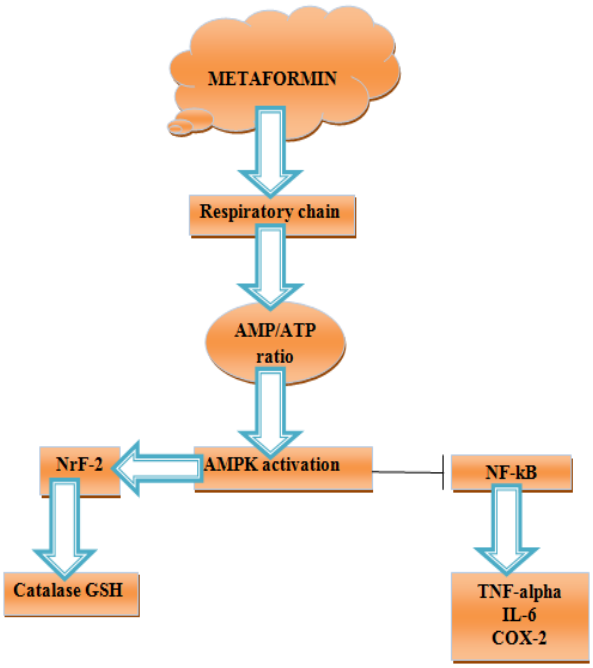

Figure 7 Molecular mechanisms of stroke outcomes via Metformin [3]

Table 4 List of drugs that effect the voltage gated channels [4]

Drug	Use
Verapamil	For managing the peripheral region
Carbamazepine	For treating the vestibular paroxysms
Cinnarizine	For managing the peripheral region
Dihydropyridines	For managing the peripheral region

CONCLUSION

This review aimed in building the bridge among neuropharmacological consequences and the variety of different drugs. Drugs affect the central nervous system upon target via different mechanisms. The neurotransmitters and neuromodulators play a crucial role in CNS of brain. The neuropharmacological studies provide novel insight for the drug design and many neurobiological activities. The computational models are developed which improved the neuropharmacological drugs and their characterization. The consequences of licit drugs improve mood, learning personality of an individual have beneficial effect on brain. On the other hand, illicit drugs induce aggression, hallucinations, lethargy, depression, irritability have hazardous effect on brain. It weakens the social network and indulged the person in the criminal activity. The government should ban on the availability of these drugs by looking at their consequences and promote the licit drugs. The future prospect of the neuropharmacological consequences of variant drugs are so wide that generate positive impact on CNS and prevent from brain disorders like stroke, Parkinson's disease due to development of new techniques as nanotechnology. These techniques help to establish such novel neuropharmacological drugs which accomplish the remedy of disease which is not possible earlier or might be possible in future.

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