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Pharmacological Networking of *Sarpagandha* (*Rauwolfia Serpenatina*) in Insomnia

Research Article

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Abstract

Sleep is a complex physiological process and insomnia is a growing issue of psycho-somatic nature. This condition is stated in Ayurveda as *anidra* and has various treatment modalities. One such single drug of choice is *Sarpagandha*, *Rauwolfia serpentina (Linn.) Benth. ex-Kurz*, indicated for such diseases. Evidence-based medicine is vital for standardization in clinical applications. Network pharmacology predicts the action mechanism of therapeutic drugs on both the interactome and diseasome levels. Objective: Understanding the activity of *sarpagandha* in insomnia through network pharmacology, involving respective pathways and gene targets to enhance the therapeutic efficacy. Material and Methods: In this study standard methods were used for collection and interpretation. Phytochemicals were collected from PubChem Compound Identifiers (CIDs). Associate targets extracted from Gene Cards using specific keyword "insomnia". Disease & protein targets acquired through Venny 2.0 and predicted through Digip pred & Swiss Target Prediction. Shared targets were uploaded onto STRING database to create the network. Using Cytoscape 3.7.1 network linking of phytochemicals & corresponding targets achieved. KEGG enrichment bubble plot analysis was conducted to interpret the signaling pathways associated with insomnia targets. Results: The study identified 21 Phyto-constituents, that significantly modulates 58 diverse target proteins related to insomnia, through 49 different pathways, among which 14 were highly significant. Two phytochemicals found to exhibit the highest degree of connectivity by linking to 16 targets which include various key receptors and enzymes. These findings align with the Ayurvedic concept of treating insomnia.

Keywords: *Sarpagandha, Rauwolfia serpentina,* Insomnia, Anidra, Network pharmacology.

Introduction

Poor health is a global crisis, impacting various aspects of life. Ayurveda mentions fundamental factors like food, sleep and celibacy play a significant role in sustenance. Sleep as an essential component is supposed to be always adequate for maintenance of health; may be because of this *Anidra* (insomnia) is not much explained in Ayurveda. The most prevalent form of sleep disorders is insomnia, with a worldwide prevalence of 30%(1,2) and 25.7% in India(3); So for management of such diseases efficient methodologies are needed for quicker research to obtain accurate results. Network pharmacology a combination of network biology and poly-pharmacology is useful in creating evidence-based medicine to determine the most effective treatment for different targets. As various patho-physiologies are involved in insomnia, to understand the appropriate drug of choice based on the presentations is need of the hour. *Sarpagandha* (*Rauwolfia serpentina (Linn.) Benth. ex-Kurz*), a well-known herb, is stated for the treatment of psycho-somatic disorders like *Anidra* (insomnia) and is chosen here for developing network to understand it's mode of action in insomnia.

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Materials and Methods

Mining of phytoconstituents and targets

A systematic collection of phytoconstituents from *Rauwolfia serpentina* sourced from multiple plant databases was conducted for network analysis. Molecular formula, molecular weights, PubChem Compound Identifiers (CIDs), and canonical SMILES were obtained from the PubChem database to enhance the understanding of the chemical composition of these phytoconstituents. Targets associated with insomnia were extracted from Gene Cards using the specific keyword "insomnia" to identify proteins relevant to this sleep disorder. Utilizing Venny 2.0, we facilitated the comparison of proteins targeted by the bioactive compounds of *Rauwolfia serpentina* as predicted by Digip pred and Swiss Target Prediction, particularly focusing on their association with disease targets. This integrated approach allows for a comprehensive exploration of potential interactions between Rauwolfia serpentina phytoconstituents and proteins implicated in insomnia, thereby elucidating their potential therapeutic relevance in managing this condition.

Protein-Protein interaction

The construction of the interaction of protein to protein (PPI) network involved the assembly of overlapping targets influenced by compounds impacting insomnia. These shared targets, identified through Venny 2.0, were uploaded onto the STRING database to create the network. The search parameters included "Homo sapiens" as the species keyword, and a confidence score threshold of 0.400 was applied to filter the interactions, ensuring reliability and relevance of the network connections. This approach facilitated the visualization and exploration of potential protein interactions associated with insomnia modulation, offering valuable insights into the underlying molecular mechanisms.

Network construction and analysis

Using Cytoscape 3.7.1, we established a network illustrating the connections between phytochemicals found in Rauwolfia serpentina and their associated targets. The network visually depicted interactions between active compounds and target genes, with unconnected nodes removed for clarity. Subsequently, the network underwent analysis using the "Network Analyzer" tool, prioritizing edge count from high to low to emphasize modulation strength. In this construction, nodes represented various components, including targets and pathways, while edges symbolized interactions among these elements. This approach provided a comprehensive overview of the relationships between *Rauwolfia serpentina* phytochemicals and their corresponding targets, facilitating the exploration of potential biological mechanisms and pathways.

Gene expression and enrichment analysis

From each category of Gene ontology, top entries were selected and analysed based on gene count, providing insights into the functional roles and associations of the genes involved. Additionally, KEGG enrichment bubble plot analysis was constructed that represent the pathways associated with targets relevant to insomnia, offering a comprehensive view of the molecular pathways implicated in this condition. This multi-faceted approach allowed for a thorough exploration of the biological processes, molecular functions, cellular components and signaling pathways underlying insomnia, enhancing our understanding of its pathophysiology and potential therapeutic targets.

Results

Mining of phytoconstituents and targets

Among 21 distinct phytoconstituents alkaloids, terpenoids, glycosides, steroids and organic compounds were found in *whole Rauwolfia serpentina* plant. The chemical composition of 21 compounds was established by using Pub chem software given in Table 1. The biochemical information was used for target prediction of Insomnia.

Table 1: Phytoconstituents with their targets

Compound	Mol Wt	Mol For	Pubchem CID	Smiles
Reserpine	608.7	C33H40N2O9	5770	COC1C(CC2CN3CCC4=C(C3CC2C1C(=O)OC)NC5=C4C=CC(=C5)OC)OC(=O)C6=CC(=C(C(=C6)OC)OC)OC
Ajmalicine	352.4	C21H24N2O3	441975	CC1C2CN3CCC4=C(C3CC2C(=CO1)C(=O)OC)NC5=CC=CC=C45
Serpentinine	685.8	C42H45N4O5	5351576	CC=C1CN2CCC3=C(C2CC1C(CC4=C[N+]5=C(CC6C(C5)C(OC=C6C(=O)OC)C)C7=C4C8=CC=CC=C8N7)C(=O)OC)NC9=CC=CC=C39
Ajmaline	326.4	C20H26N2O2	6100671	CCC1C2CC3C4C5(CC(C2C5O)N3C1O)C6=CC=CC=C6N4C
Serpentine	349.4	C21H21N2O3	73391	CC1C2C[N+]3=C(CC2C(=CO1)C(=O)OC)C4=C(C=C3)C5=CC=CC=C5N4
Yohimbine	354.4	C21H26N2O3	8969	COC(=O)C1C(CCC2C1CC3C4=C(CCN3C2)C5=CC=CC=C5N4)O
Rescinnamine	634.7	C35H42N2O9	5280954	COC1C(CC2CN3CCC4=C(C3CC2C1C(=O)OC)NC5=C4C=CC(=C5)OC)OC(=O)C=CC6=CC(=C(C(=C6)OC)OC)OC
Rescinnamidine	636.7	C35H44N2O9	184180	COC1C(CC2CN3CCC4=C(C3CC2C1C(=O)OC)NC5=C4C=CC(=C5)OC)OC(=O)CCC6=CC(=C(C(=C6)OC)OC)OC
Reserpiline	412.5	C23H28N2O5	67228	CC1C2CN3CCC4=C(C3CC2C(=CO1)C(=O)OC)NC5=CC(=C(C=C45)OC)OC
Deserpidine	578.7	C32H38N2O8	8550	COC1C(CC2CN3CCC4=C(C3CC2C1C(=O)OC)NC5=CC=CC=C45)OC(=O)C6=CC(=C(C(=C6)OC)OC)OC
Isoajmaline	326.4	C20H26N2O2	6325415	CCC1C2CC3C4C5(CC(C2C5O)N3C1O)C6=CC=CC=C6N4C
Rauwolscine	354.4	C21H26N2O3	643606	COC(=O)C1C(CCC2C1CC3C4=C(CCN3C2)C5=CC=CC=C5N4)O
Sarpagine	310.4	C19H22N2O2	12314884	CC=C1CN2C3CC1C(C2CC4=C3NC5=C4C=C(C=C5)O)CO
Tetraphyllicine	308.4	C20H24N2O	6436266	CC=C1CN2C3CC1C4C2CC5(C3N(C6=CC=CC=C65)C)C4O
Kaempferol	286.24	C15H10O6	5280863	C1=CC(=CC=C1C2=C(C(=O)C3=C(C=C(C=C3O2)O)O)O)O
Rutin	610.5	C27H30O16	5280805	CC1C(C(C(C(O1)OCC2C(C(C(C(O2)OC3=C(OC4=CC(=CC(=C4C3=O)O)O)C5=CC(=C(C=C5)O)O)O)O)O)O)O)O
Gallic acid	170.12	$C_7H_6O_5$	370	C1=C(C=C(C(=C1O)O)O)C(=O)O
Digallic acid	322.22	C14H10O9	341	C1=C(C=C(C(=C1O)O)O)C(=O)OC2=CC(=CC(=C2O)O)C(=O)O
Sallicylic acid	138.12	$C_7H_6O_3$	338	C1=CC=C(C(=C1)C(=O)O)O
Methyl Salicylate	152.15	$C_8H_8O_3$	4133	COC(=O)C1=CC=CC=C1O
Acetyl salicylic acid	180.16	$C_9H_8O_4$	2244	CC(=O)OC1=CC=CC=C1C(=O)O

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Using "Insomnia" as a keyword, from the Gene Card database a total of 6,509 genes were retrieved. From these, the selected top 500 genes were compared with the target genes of the active elements to identify potential insomnia target genes for each active ingredient using Venny 2.0 (Figure 1). After a thorough analysis, 58 potential insomnia-related target genes for Rauwolfia serpentina were identified, as detailed in Supplementary Table 2.

Construction and Analysis of Target Protein PPI Network

The target proteins associated with their matching active elements were loaded to STRING Version 10.5 (http://string-db.org/) for constructing the PPI (Protein-Protein Interaction) network. For the analysis, protein interaction data with medium confidence scores (0.400) were selected (Figure 2). The resulting network comprises 58 nodes and 359 edges, where all nodes are interconnected. In this network, target proteins are represented by nodes, and interactions among these proteins are represented by edges. A higher degree indicates a stronger relationship between the corresponding proteins to respective node, signifying that these target proteins play a crucial role in the whole network of interaction and recognizing them as key target proteins.

Network construction and analysis

The network analysis revealed potential relationships between compounds and targets, providing insights into the pharmacological mechanisms underlying these compounds. Notably, Rauwolscine and yohimbine emerged as central nodes within the network, exhibiting the highest degree of connectivity by linking to 16 targets. These targets include key receptors and enzymes such as DRD2, HTR2A, HTR1A, OPRM1, GABRB3, CYP2D6, SLC6A3, DRD1, HTR2C, PDE2A, PSEN2, SLC6A4, PER2A, CNR1, SELC, and ICAM1. The prominence of these compounds suggests their potential as significant pharmacological agents or targets, warranting further investigation into their therapeutic implications.

Gene expression and enrichment analysis

In Gene Ontology (GO) analysis, we identified a substantial number of biological processes (567), cellular components (51) and molecular functions (49) with an adjusted medium confidence level (0.400). Notably, many of the biological processes were associated with critical functions such as chemical synaptic transmission, central nervous system development and regulation of nervous system processes, highlighting their significance in neuronal function and development. Cellular component analysis revealed that these processes predominantly occur in cell junctions, neuron projections, Wnt signalosomes, neuromuscular junctions, and GABA-A receptor complexes, underscoring the importance of these cellular structures in neuronal communication and function. In terms of molecular functions, the enriched terms were primarily related to dopamine binding, dopamine neurotransmitter activity and G protein-coupled receptor activity, suggesting the involvement of these molecular mechanisms in neuronal signaling and neurotransmission. (Figure 4).

Additionally, 49 significantly enriched pathways were identified by Kyoto Encyclopaedia of Genes and Genomes, KEGG pathway analysis with particular emphasis on the Neuroactive ligand-receptor interaction pathway, indicating the impact of bioactive compounds from Rauwolfia serpentina on neuronal signaling pathways. Furthermore, among the enriched KEGG pathways, 14 pathways were specifically associated with Insomnia. These pathways play direct and indirect roles in initiating and regulating sleep responses in the body, shedding light on the complex molecular mechanisms underlying sleep disorders like Insomnia. (Figure 5)

Figure 1: Common targets between compounds and Disease target

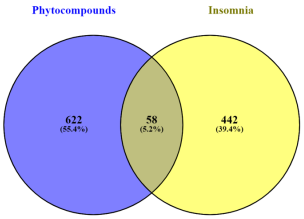
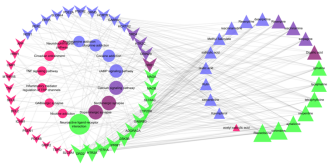


Figure 2: Protein-Protein interactions

Figure 3: Network construction between phytocompounds, disease targets and pathways.

A) Degree sorted circle layout.



B) Apply preferred layout.

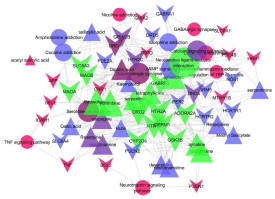


Figure 4: Gene enrichment analysis

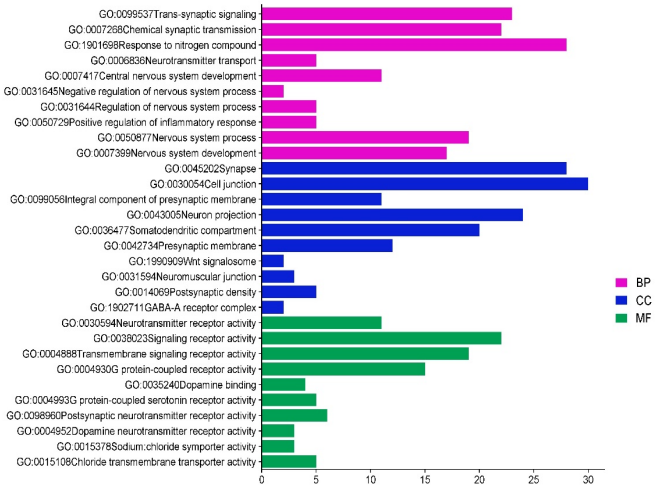
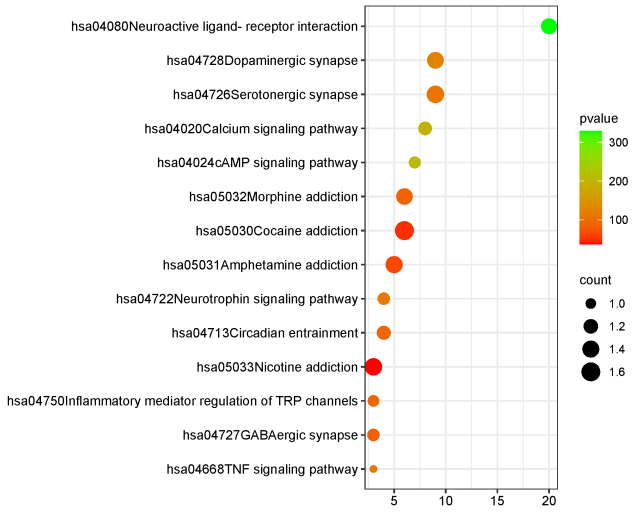


Table 2: KEGG analysis of selected pathways

Term ID	Term description	OGC	BGC	FDR	Proteins
hsa04080	Neuroactive ligand-receptor interaction	20	329	1.7E-18	DRD4, MTNR1B, HTR2C, DRD5, GRM5, GABRB3, HTR1A, DRD2, CNR1, DRD1, TSPO, HRH1, HCRTR1, GABRA1, OPRM1, GRIK2, HTR2A, GRIN2B, HCRTR2, ADORA2A
hsa04726	Serotonergic synapse	9	108	0.0000000092	SLC6A4, HTR2C, APP, GABRB3, HTR1A, MAOA, MAOB, HTR2A, CYP2D6
hsa04728	Dopaminergic synapse	9	126	0.0000000223	DRD4, SLC6A3, DRD5, GSK3B, MAOA, DRD2, MAOB, DRD1, GRIN2B
hsa04020	Calcium signaling pathway	8	191	0.00000642	HTR2C, DRD5, GRM5, DRD1, HRH1, HTR2A, NOS1, ADORA2A
hsa05032	Morphine addiction	6	88	0.0000151	GABRB3, PDE2A, PDE4B, DRD1, GABRA1, OPRM1
hsa05031	Amphetamine addiction	5	65	0.0000643	SLC6A3, MAOA, MAOB, DRD1, GRIN2B
hsa04024	cAMP signaling pathway	7	207	0.0000912	DRD5, HTR1A, PDE4B, DRD2, DRD1, GRIN2B, ADORA2A
hsa04713	Circadian entrainment	4	91	0.0034	PER2, MTNR1B, GRIN2B, NOS1
hsa05030	Cocaine addiction	6	49	0.00000107	SLC6A3, MAOA, DRD2, MAOB, DRD1, GRIN2B
hsa05033	Nicotine addiction	3	37	0.0038	GABRB3, GABRA1, GRIN2B
hsa04722	Neurotrophin signaling pathway	4	112	0.0057	GSK3B, PSEN1, PSEN2, BCL2
hsa04727	GABAergic synapse	3	85	0.02	GABRB3, GABRA1, SLC6A1
hsa04668	TNF signaling pathway	3	111	0.0342	ICAM1, SELE, TNF
hsa04750	Inflammatory mediator regulation of TRP channels	3	92	0.0236	HTR2C, HRH1, HTR2A

Figure 5: KEGG analysis of selected pathways



Discussion

Understanding the human genetic base of complex disorders is a crucial objective in biomedical research. With the rapid progression of cross-disciplinary studies, it is essential to transition from a conceptual understanding of diseases to a systematic drug and disease network. This shift is necessary for a comprehensive understanding of the molecular foundations of their interconnections, facilitating the appropriate selection of treatment methods. Recent approaches on computational SysBiomics have enhanced the understanding of multifaceted diseases by identifying disease-related genes and elucidating disease mechanisms. Parallel methods have been effectively used to analyse drug responses in various pathophysiological processes, including diabetes type 2, immunology, and metastasis of breast cancer (4).

Insomnia is a prevalent condition, primarily characterized by a hyperarousal mechanism. Hyperarousal in physiological, emotional, or cognitive networks is supposed to interfere with regulatory processes of sleep, leading to a wide array of adverse consequences. According to a systematic review on sedative-hypnotic drugs, abrupt discontinuation of these therapies can result in several side effects, such as physical and psychological dependence, habituation, daytime anxiety or drowsiness, daytime cognitive and psychomotor impairment, and rebound insomnia(5).

Human body requires phytochemicals, especially antioxidants to protect cells from free radical damage, enhance and regulate metabolism and to promote enzyme activity. These molecules may improve health, impacting neuro-degeneration through binding to transcription factors, targeting signaling pathways and altering epigenetics. In Ayurveda the drugs are administered as a whole product, rather than extracts and is believed that the target action of each element

will help in the collective action. *Sarpagandha* (*Rauwolfia serpentina)* when administered as a whole herb with proper dosage provide balanced effect and minimize the side effects.

Among several phytochemicals present in *Sarpagandha* (*Rauwolfia serpentina)*, 21 of them were chosen to study their effect on insomnia. As a result, we discovered 49 pathways, among them 14 were highly significant through which 21 phytochemicals operate on 58 target genes associated with insomnia. The major pathways were neuroactive ligand-receptor interaction, calcium signaling pathway, dopaminergic synapse, serotonergic synapse, cAMP signaling pathway, amphetamine addiction, cocaine addiction, morphine addiction, and circadian entrainment, but it also showed action through neurotrophin signaling pathway, GABAergic synapse, nicotine addiction, TNF signaling and Inflammatory mediators regulate TRP channels pathway. As we know that process S and process C regulates sleep; disturbances in those cause insomnia; So, the pathways mentioned here contribute to the regulation of various activities by acting on those processes and genes. Similarly, it may follow the Ayurvedic view of balancing *dosha* (basic humors of body) and *manas* (mind) for induction of sleep.

The pathways found in the *Sarpagandha* (*Rauwolfia serpentina)* have action on various processes explained earlier. Neuroactive ligand-receptor interaction pathway involves the interaction between neurotransmitters (neuroactive ligands) and their respective receptors in the nervous system. Neurotransmitters such as serotonin, dopamine and GABA bind to specific receptors on neurons, initiating signaling cascades that regulate various physiological processes like S and C, i.e. sleep-wake cycles(6,7). Regulation of neuroactive ligand-receptor interactions can balance the neurotransmission and contribute for improving sleep. Here, various phytochemicals showed the activity on this pathway which will be acting on genes. (As shown in Supplementary Table)

Serotonin is a neurotransmitter involved in regulating mood, cognition and sleep. Once released from presynaptic neurons, binds to serotonin receptors on postsynaptic neurons in the serotonergic synapse. This activation of serotonin receptors modulates neuronal activity and influences sleep-wake cycles. Imbalances in serotonin signaling within the serotonergic synapse have been implicated in sleep disorders, including insomnia(8,9). Various phytochemicals found in *Sarpagandha* (*Rauwolfia serpentina)* showed the activity on serotonin signaling pathway which will be acting on several genes (as shown in Supplementary Table) contributing for improving sleep.

Dopamine as a neurotransmitter and Dopaminergic signaling activity are involved in reward, motivation, arousal and movement control, all of which are closely linked to sleep regulation. From presynaptic neurons dopamine is released and binds to dopamine receptors on postsynaptic neurons in the dopaminergic synapse(8,10,11). Regulation of dopamine signaling in the dopaminergic synapse can improve the sleep patterns. As per this study, various phytochemicals showed the activity on this pathway which will be acting on respective genes (as shown in Supplementary Table) involved in sleep regulation.

Cocaine is a stimulant drug that affects neurotransmitter systems, including those involved in sleep regulation. Chronic cocaine use can lead to alterations in dopamine signaling and other neurotransmitter systems, resulting in sleep disturbances and insomnia(12). Cocaine is also known to increase dopamine release from striatal terminals and dopamine is known for controlling sleep wake cycle(13). The involvement of cocaine pathway in *Sarpagandha* (*Rauwolfia serpentina)* was found to be moderate, stating that this may help in initial induction of sleep and may not interfere with sleep regulation, preventing the sleep disturbances.

In Calcium signaling pathway, Calcium ions play a vital role in synaptic plasticity, neurotransmitter release, and neuronal excitability. MAPK signaling pathways are proved for sleep regulation(14) and published data has also identified the signaling pathways between Ca(2+) and MAPK has both interactions directly and indirectly(15). Regulation of calcium signaling pathways can balance neuronal function and contribute in improving sleep(16).

Morphine, an opioid drug, affects neurotransmitter systems involved in pain modulation and sleep regulation. Chronic morphine use can lead to tolerance, dependence, and alterations in sleep architecture, contributing to insomnia. However, excess GABA can cause drowsiness and daytime sleepiness. GABAergic neurons can mediate to reduce the inhibitory synaptic transmission leading in indirect excitation of VTA dopamine neurons by Morphine(17). This route was found to be minimally involved, suggesting its action in sleep induction and not sleep alteration.

Amphetamines are stimulant drugs that increase the neurotransmitters release such as dopamine and norepinephrine and may help in the similar action as that of the latter(18).

The cyclic adenosine monophosphate (cAMP) signaling pathway controls several cellular processes with gene expression, neuronal excitability, and neurotransmitter release(19). A study suggested that sleep deprivation can disrupt hippocampal function by increasing PDE4 activity, conveying that drugs which enhance cAMP signaling could be of potential therapeutic approach(20). Thus identified cAMP signaling pathway in Sarpagandha (*Rauwolfia serpentina)* can balance sleep-wake cycles.

Circadian entrainment pathway regulates the body's internal clock and synchronizes physiological processes with the external environment, including the sleep-wake cycle(21).

A usual characteristic of addictive substances, including nicotine, is their ability to increase release of dopamine in the nucleus accumbens (NAc), thereby affecting the mesolimbic area, corpus striatum, frontal cortex, and reward system(22,23). However, the involvement of this pathway is minimal in sleep

induction, suggesting it may facilitate sleep without significantly altering sleep patterns.

Neurotrophins, a family comprising of trophic factors, are essential for neural cell differentiation and survival. Neurotrophin/Trk signaling regulates various intracellular signaling pathways, including the PI-3 kinase pathway, MAPK pathway and PLC pathway(24). Neurotrophic factors in the NGF family, similar to BDNF, act on specific neurons in the central and peripheral nervous systems. Evidence indicates a mutual relationship between BDNF and the circadian rhythm; also, these BDNF and TrkB expressed in the suprachiasmatic nucleus (SCN) regulate the central master clock in mammals and other brain regions(25).

In the central nervous system of mammals within the GABAergic synapse, GABA is the prevalent repressive neurotransmitter(26). GABAergic cells present in the anterior hypothalamus and basal forebrain are pivotal for sleep regulation. These cells demonstrate increased action throughout non-rapid eye movement (NREM) sleep compared to REM sleep or waking, characterized by higher discharge rates and elevated GABA release(27).

A critical cytokine such as Tumor necrosis factor (TNF) can activate a broad spectrum of intracellular signaling pathways, containing those involved in apoptosis, cell existence, inflammation, and immunity(28). TNF promotes sleep by influencing multiple synaptic functions, and its role in sleep and plasticity suggests the existence of biochemical regulatory mechanisms that integrate TNF into the sleep regulation network(29).

The study also highlights the inflammatory intermediary regulation of TRP channels. These channels, which respond uniquely to temperature changes, can be indirectly controlled by inflammatory mediators like PGE2, bradykinin, NGF, ATP, and proinflammatory cytokines(30). Prostaglandin E2 (PGE2), the most biologically active prostaglandin, plays roles in smooth muscle relaxation, sleep cycle regulation, inflammation, fertility and maintaining gastric mucosal integrity(31). Previous research has shown that NGF application in the nucleus pontis oralis (NPO) persuades REM sleep by binding to Trk receptors in neurons and axon terminals(32).

In Ayurveda *Sarpagandha (Rauwolfia serpentina)* is mentioned under the category of *nidrajanaka* (sleep inducing and regulating) drugs, with its effective qualities helps in breaking down the pathophysiology of *anidra* (insomnia) and regulates sleep. A previously published data documented the understanding of pathophysiology of insomnia using neurotransmitter sleep theories; it is stated that the involvement of *Tamo Dosha* and *Kapha Dosha* in *nidra* (sleep) can be correlated to the action of Serotonin, like-wise, *Shrama* to Adenosine and serotonin, and *Svabhava* to Melatonin. While factors contributing to *anidra* such as *Vata–Pitta Vriddhi* (Increased state) can be correlated to the activity of GABA, noradrenaline and acetylcholine, *Manastapa* to Dopamine and serotonin, *Kala* to Melatonin, serotonin, and dopamine, *Kshaya* to Atrophic changes affecting all neurotransmitters, *Karya* to Dopamine and serotonin and *Abhighata* - Local injury to sleep-promoting areas hampering sleep patterns(33). It has also been suggested that messenger RNA, tRNA and protein have characteristics and attributes that represent *Vata* (transmission of information), *Pitta* (transformation), and *Kapha* (structure) at the cellular level. Additionally, some studies have indicated that the genotype corresponds to Ayurvedic *Janma Prakriti* and the phenotype to Ayurvedic *Deha Prakriti*(34).

From above explained theories and networking findings we can opine that, serotonin pathway activity can be considered as *kala* (*ratriswabhava*), *shrama*, *tama-kapha* and *manasa* regulation, which would be acting through Ajmaline, Serpentine, etc., on SLC6A4, HTR2C, GABRB3, CYP2D, etc. genes and also the factors like *kala*, *manastapa*, *karya* can be correlated to dopaminic activity in *anidra* which would be acting through phytochemicals like Isoajmaline, Tetraphyllicine, etc., by regulating DRD4, SLC6A3, DRD5, GSK3B, etc., genes. As *prakriti* is one of the *nidana* (contributing factor) in *anidra*, it also resembles with contemporary genetic or hereditary involvement in insomnia. Further studies are essential to correlate the fundamentals of different sciences for better understanding and practical implementation.

Conclusion

Sleep being the most important physiological phenomenon, nourishes the body, maintains hormonal balance, improves memory and minimizes the occurrence of various complications like psychosis, Alzheimer's, mania, anxiety. Ayurveda also emphasizes the importance of sleep in the sustenance of life, various drugs have been stated for such psychosomatic conditions and the need of the era is to understand the appropriate drug for selection in different presentations of insomnia. *Sarpagandha* (*Rauwolfia serpentina)* one potent *nidrajanaka* (sleep inducing and regulating) drug was found to act through 49 pathways, targeting 58 and more genes proving its efficacy in promoting sleep. Research work on clinical studies related to this perspective is ongoing. Further research is necessary to find out and conclude the mode of action of such drugs in other psychosomatic disorders.

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