Journal of Ayurveda and Integrative Medicine 14 (2023) 100720

Contents lists available at ScienceDirect

Journal of Ayurveda and Integrative Medicine

journal homepage: http://elsevier.com/locate/jaim

Review Article

Role of Ayurveda in the management of psychotic disorders: A systematic review of clinical evidence

Kavyashree Kulamarva, Venkataram Shivakumar*, Umesh Chikkanna, Kishore Kumar Ramakrishna, Hemanth Bhargav, Shivarama Varambally

Department of Integrative Medicine, National Institute of Mental Health and Neurosciences (NIMHANS), Bengaluru, 560029, India

ARTICLE INFO

Article history:
Received 14 January 2022
Received in revised form
11 March 2023
Accepted 29 April 2023
Available online xxx

Keywords:
Psychotic disorders
Schizophrenia
Unmada
Ayurveda
Systematic review

ABSTRACT

Background: Despite advancements in the treatment of psychosis, many patients continue to experience persistent symptoms and relapses during antipsychotic treatment, particularly when they fail to adhere to prescribed medications. Ayurveda explains psychotic disorders as "*Unmada*" and describes various treatment protocols. Although these therapies and methods have been in practice for several years, systematic evidence has not been generated for the same. Thus, in the current review an attempt has been made to illustrate currently available clinical trials on Ayurveda management of psychosis.

Methods: We identified 23 studies by literature search in PubMed Central, Cochrane Library and AYUSH Research portal. Out of these, 21 were retrieved after systematic deduplication. After excluding nine studies, 12 studies were included for review.

Results: Total of 12 articles comprising 10 clinical trials and 2 case reports were reviewed. Most of the studies demonstrated significant improvement in psychopathology assessed through various symptom rating scales.

Discussion: The role of Ayurveda, in the treatment of psychosis is least explored. Currently available studies on the effect of Ayurveda treatment on psychosis are very less in number to draw a valuable conclusion. Hence there is a large scope for conducting neurobiologically informed clinical research in the management of psychotic disorders using Ayurvedic approaches.

1. Background

Psychotic disorders are severe mental disorders that cause abnormal thinking and perceptions. Delusions and hallucinations are the two main symptoms of psychosis. People with psychosis may also lose touch with reality [1]. The collective incidence of all psychotic disorders in 2002–2017 was 26·6 per 100 000 people [2]. According to a systematic review published in 2018, lifetime prevalence of psychosis was 7.49 per 1000 [3]. Schizophrenia is the most prevalent functional psychotic disorder among various psychotic spectrum disorders and ranks among the top 10 global burdens of disease identified by the WHO [4]. In addition to the direct burden, there is substantial burden on the families who care for the sufferers. The management of schizophrenia is currently aimed at early diagnosis & treatment initiation, prevent relapses, provide rehabilitation services and reintegrate the ill persons into the community so that they can lead as normal a life as possible [5].

Despite much progress, the pharmacological treatment of psychotic disorders is often unsatisfactory [6]. Even with advancement in the treatment of schizophrenia, many patients continue to experience persistent symptoms and relapses during antipsychotic treatment, particularly when they fail to adhere to prescribed medications [7]. One of the main reasons for non-adherence to medications is the side-effects associated with antipsychotics [8]. In search of a treatment devoid of side-effects, a significant number of patients experiencing psychosis turn to nonconventional medications or therapies, aiming to reduce undesired adverse effects and enhance their chances of a more effective recovery [9].

Ayurveda is a traditional system of medicine originating from India. It focuses on balancing the lifestyle and biorhythms through the application of herbal formulations and detoxification procedures. It has enormous potential to treat many disorders of the body and mind. Ayurveda understands schizophrenia spectrum and other psychotic disorders as *Unmada*. *Unmada* is described in the Ayurveda texts as a disorder that manifests when the physical and

* Corresponding author.
E-mail: drshiv.nimhans@gmail.com
Peer review under responsibility of Transdisciplinary University, Bangalore.

https://doi.org/10.1016/j.jaim.2023.100720

psychological stressors vitiate the humors- *Vata, Pitta*, and *Kapha*, displace them from their original site and expulse upward to the *manas* (mind) resulting in a wide range of physical and psychological symptoms [10]. According to ancient Ayurveda text *Charaka Samhita*, *unmada* can be classified into five subtypes: 1) *Vataja unmada* (*unmada* due to vitiation of vata humor), 2) *Pittaja unmada* (*unmada* due to vitiation of pitta humor), 3) *Kaphaja unmada* (*unmada* due to vitiation of kapha humor), 4) *Sannipataja unmada* (*unmada* due to vitiation of all three humors), 5) *Agantuja unmada* (*unmada* due to exogenous causes like non-observance of spiritual disciplines or supernatural things). Although symptomatic manifestations vary according to the *dosha* (humor) involved, the following aspects of an individual personality are commonly affected in all three types of *Unmada*: *Mana*-thoughts/mental faculties, *Buddhi*-intellect, *Samjna*-awareness, *Jnana*- orientation, *Smriti*-memory, *Bhakti*- desire, liking or attitude towards the society, *Sheela*-habits and temperament, *Cheshta*-psychomotor activities and *Achara*-routine activities of daily living [11]. These changes may manifest acutely or take a chronic progressive course, resulting in the affected person losing touch with reality and his ability to sustain himself in society.

Ayurveda also explains a systematic treatment protocol for *Unmada* which is based on three principles: 1) *Daivavyapashraya* (spiritual/divine therapy), 2) *Yukti vyapashraya* (therapy based on clinical reasoning) and 3) *Satwavajaya* (psychotherapy). The major focus in acute symptomatic phase is on the *Yuktivyapasraya chikitsa*, which involves treatment in the following phases: 1) *Deepana* and *Pachana* (correction of digestive fire), 2) *Snehapana* (Oral administration of medicated clarified butter or ghee), 3) *Mridu sodhana* (mild purification by induced emesis or purgation), 4) *Samsarjana krama* (Dietetic regimen). The aim of this treatment is to balance vitiated humors and facilitate the normal psychological functions. Further treatment is planned to modulate the residual morbid humors and for maintenance purpose, which involves 1) "*Basti*" (medicated enema), 2) "*Shirovirechana*" (medicated nasal errhines) and 3) "*Samjna prabodhana*" (medications to improve awareness and orientation) [12]. Along with these, several poly herbal formulations having disease modifying effects are also administered for a prolonged duration.

Ayurveda has numerous therapeutic formulations and treatment protocols described for psychotic disorders/schizophrenia. Although these therapies and methods have been in practice for several years, systematic evidence has not been generated for the same. Thus, in the current review an attempt has been made with an objective of summarizing currently available clinical trials exploring Ayurveda treatment protocols in psychotic disorders and evaluating them with conventional treatment procedures.

2. Methods

Literature Search and Study Selection: We identified the studies by literature search in PubMed Central, Cochrane Library and AYUSH Research portal (https://ayushportal.nic.in/). The key words that were used for the search are, "Unmada", "psychosis AND Ayurveda", "psychosis AND complementary and alternative medicine". Total 23 studies were identified in different databases and one study was identified from another source (NIMHANS journal). Out of the these, 21 were retrieved after systematic deduplication.

Subsequently, review articles, unpublished manuscripts/dissertations, conceptual/survey studies, studies with insufficient/missing data, conference abstracts, book chapters, clinical trial registrations, comments/addenda/corrigenda, and articles in languages other than English were excluded. The remaining 12 studies were published from 1976 to 2019 including randomized control trials with either active or placebo controland non-randomized trials (observational, prospective, or retrospective) c) Single case reports and case series were included for further review. The details of the screeningand inclusion/exclusion of articles are depicted in the PRISMA flowchart (Fig. 1). The findings from the 12 studies included in this review are summarized in Table 1.

3. Results

A Total of 12 articles comprising of ten clinical trials and two case reports were reviewed. Majority of the studies demonstrated significant improvement in psychopathology assessed through various symptom rating scales. A double-blind study on *Brahmyadi yoga (B. yoga)* and *Tagara* showed significant improvement in both chlorpromazine (control group) and *B. yoga* group compared to *Tagara* and placebo groups suggesting non-inferiority effect of *B. yoga* [13]. A pilot study conducted on the role of *Brahmyadi yoga* in chronic *unmada* (schizophrenia) in 14 patients showed statistically significant improvement in positive and negative scores of symptoms rating scale (Rockland 1965) [14]. Clinical assessment of *medhya* drugs (Ayurveda psychotropic drugs) in the management of psychosis showed improvement in Psychosis Symptom Grading Scale [15]. Another preliminary study on indigenous psychotropic drugs showed significant improvement in 17 refractory cases of schizophrenia as evidenced by reduction in BPRS scores [16].

A randomized clinical trial on Ayurveda treatment in acutely ill patients (active psychotic symptoms for a minimum of one month) with schizophrenia showed significant improvement on BPRS scores and some of the psychological (cognitive) tests. But the difference between Ayurveda treatment group and chlorpromazine (CPZ) group was not statistically significant in the final assessment. However, significant improvement in the Ayurveda group was seen on few neurocognitive tests as compared to the CPZ group [17]. In a study evaluating the clinical efficacy of *Smriti sagara rasa* in cases of residual schizophrenia, eleven out of thirty patients (36.67%) showed a significant improvement and an approximately similar number (33.33%) showed moderate improvement after three months of treatment [18]. A comparative study on *Unmada gaja kesari rasa* along with conventional treatment in 64 schizophrenia patients for a period six months including three follow ups showed sustained improvement in negative symptoms, general psychopathology, and on total PANSS score while the impact on positive symptoms were insignificant. Response in the add-on group with *Unmada gaja kesari rasa* and conventional treatment was more in comparison to stand-alone *Unmada gaja kesari rasa* and conventional treatment [19]. In another clinical trial on *B. yoga* (500 mg 2 capsules TID) for six-months showed 67.5% improvement in BPRS, 67.1% in SANS and 66.7% in SAPS. The overall improvement in all clinical parameters were significant [20]. A single case report on add-on effect of Brahmi tablets (each tablet containing 250 mg of Brahmi extract) with olanzapine showed reduction in PANSS and BPRS scores by reducing the psychopathology [21]. Another case report on two cases of undifferentiated schizophrenia showed complete reduction in PANSS scores in one patient after Ayurveda treatment [22].

A randomized double-blind placebo-controlled study on adjunctive use of a standardized extract of *Withania somnifera* (*Ashwagandha* 1000 mg/day) on symptom exacerbation in schizophrenia showed a significant reduction in PANSS negative, general, and total symptoms except for positive symptoms when compared to placebo. Perceived Stress Scale (PSS) scores also reduced significantly with *Ashwagandha* (*W. somnifera*) extract (WSE) and CRP and S100B (neuroinflammatory marker) levels declined more in the WSE group but not statistically significant when compared to the placebo [23]. Another similar clinical trial on the effect of WSE on depression and anxiety symptoms in persons with schizophrenia,

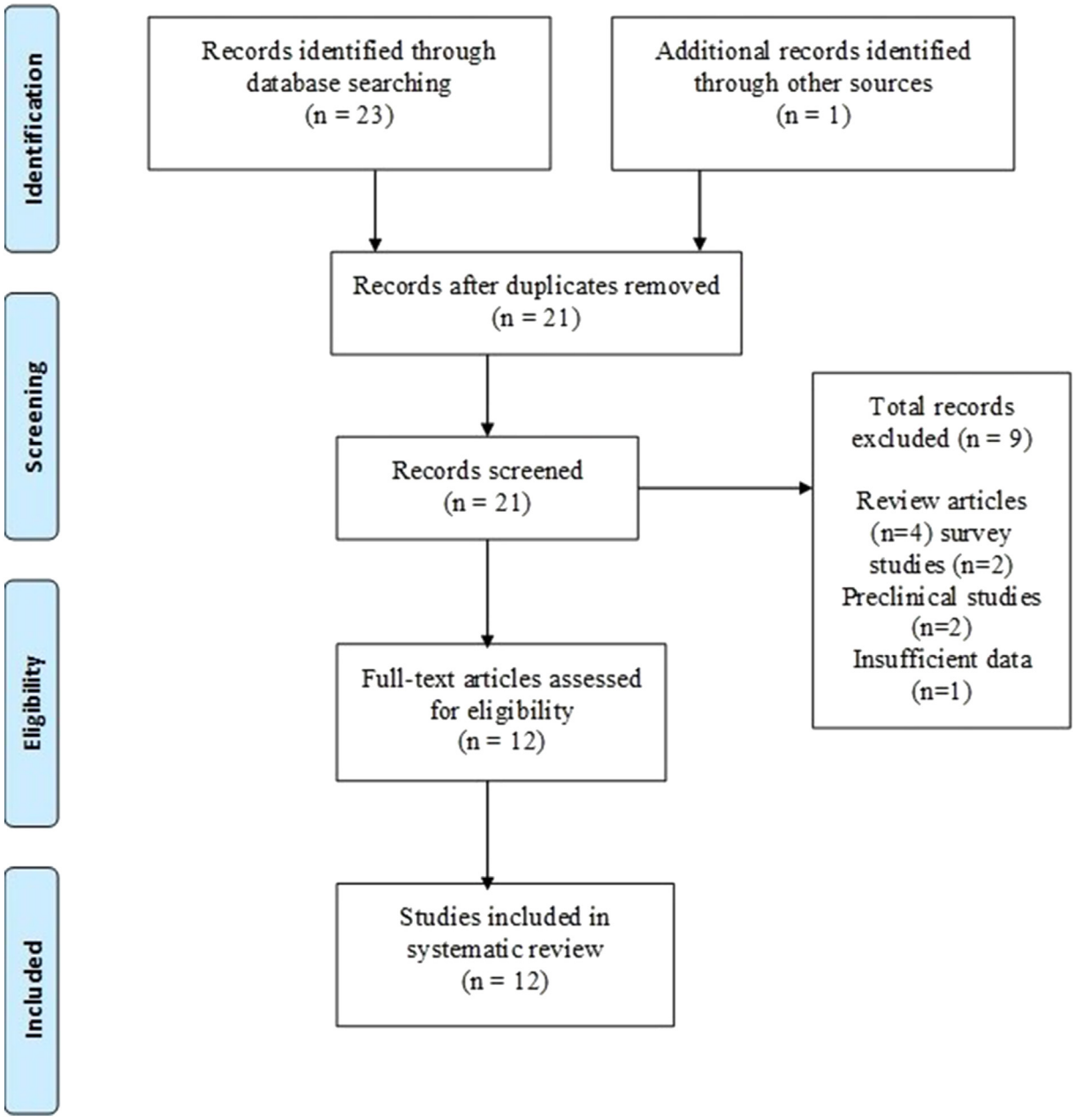

Fig. 1. PRISMA flow chart- Details of screening, inclusion/exclusion of articles.

reported a significant improvement in depression scores in WSE (0.71 ± 0.97) compared to placebo (0.06 ± 0.93). The mean change in anxiety-depression cluster scores for patients who received WSE were also significantly higher (2.86 ± 2.56) than mean change scores for patients who received a placebo (1.19 ± 2.32). Medium treatment effect sizes of 0.683 (95% CI, 0.16 to 1.21) and 0.686 (95% CI, 0.16 to 1.21) supporting WSE over placebo were observed for depression single-item and anxiety-depression cluster scores, respectively [24].

4. Discussion

Out of 12 studies, five were on polyherbal formulations (*B. yoga*, *medhya* drugs and GK022), three studies were on single herb extracts (*Ashwagandha & Brahmi*) and the remaining two studies were on herbomineral compounds. Among five studies on polyherbal formulations, two studies have included *panchakarma* procedures. The most studied polyherbal formulation was *B. yoga* followed by *Ashwagandha*. *B. yoga* as an adjuvant was found to be effective in the treatment of schizophrenia, whereas GK022 was found to be beneficial in untreated cases. A polyherbal formulation of *medhya* drugs also showed beneficial effects in psychosis. *Unmada gajakesari rasa* and *S. sagara rasa* were beneficial in negative symptoms and residual schizophrenia, respectively. Polyherbal formulations along with *Panchakarma* therapy showed improvement in undifferentiated schizophrenia; the result was comparable with that of CPZ. *Ashwagandha* as an add-on helped in improving negative symptoms, anxiety as well as depression. *Brahmi* was also found to be effective in paranoid schizophrenia when used as an adjuvant.

In addition to the differences in the composition of medications and treatment protocols, the studies also differed with respect to

Table 1
Summary of findings from 12 studies.

Serial No.	Reference	Study design	Treatment	Outcome
1.	A.S Mahal et al., 1976	Double Blind Randomized Controlled Trial 4 groups, 27 subjects in each group n = 108	Single drug + polyherbal formulation: *Tagara*-8gm *Brahmyadi yoga*-8gm, Placebo- 8 gm, Chlorpromazine-200mg. 2nd month- 12 gm for 3 groups, CPZ,300 mg- control group Duration-2 months	*Brahmyadiyoga* is significantly more effective in reducing the mental symptoms than Tagara and Placebo. But it was not effective than CPZ
2.	M G Ramu et al., 1983	Single arm clinical trial (Pilot study) n = 14	Polyherbal formulation: *Brahmyadi yoga* 8-16 gm, Duration-3 months	11 out of 14 patients showed improvement in Psychiatric symptom rating scale
3.	S. C. Dash, S. N. Tripathi and R. H. Singh, 1983	Single arm clinical trial n = 16	Polyherbal formulation: Decoction- 50 ml in 2 divided doses (12 gm of *Shankhapushpi Jatamamsi Brahmi Ashwagandha Vacha*) Duration- 6 weeks	Drug has potential effect on psychosis noted in Psychotic symptom grading scale and can be used for longer duration without side effects
4.	M.D. Parikh et al., 1984	Non-Randomized clinical trial n = 39 (a = 17 refractory schizophrenia, b = 22 Untreated cases)	Polyherbal formulation: Tablet GK022 Group A- 2 BD increased to 5 TDS + Antipsychotic treatment; Group B- 3 QDS increased to 6 QDS Duration- 6 weeks	The drug was found to be effective in group A showing reduction in BPRS. Result of group B was also equally encouraging.
5.	Ramu MG et al., 1992	Randomized clinical trial n = 36 (Trial-18, Control-18)	Purificatory procedure + polyherbal formulation: Trial-Ayurveda Purificatory procedure + Palliative care Control- CPZ 300–600 mg, Tab THP 2 mg, Inj/Tab Diazepam sos Duration- 28 days	Significant improvement on neurocognitive tests. The two groups did not significantly differ in the final assessment on any of the tests indicates that the Ayurvedic treatment was almost as effective as the CPZ treatment.
6.	J.S. Tripathi and R.H. Singh 1993	Non- randomized clinical trial n = 30	Herbomineral compound: *Smriti sagara rasa* 250 mg thrice a day with honey Duration-3 months	*Smrti sagara rasa* is a safe and moderately effective indigenous remedy for residual schizophrenia
7.	Onkar Chaudhari, S. Gupta and R. H. Singh 2002	Non- randomized clinical trial n = 64	Herbomineral compound: A. *Unmada gaja kesari rasa* (125 mg 1cap. TID)-22 B. *Unmada gaja kesari rasa* + Conventional treatment-17 C. Conventional Treatment-10 Duration- 3 months	*Unmada gaja kesari rasa* showed sustained relief on the negative symptom score of PANSS and general psychopathology score and on the total PANSS score while the impact on positive symptoms were insignificant.
8.	B·C.S. Rao et al., 2011	Non- randomized clinical trial n = 27	Polyherbal formulation: *Brahmyadi yoga*-500mg 2 TID Duration-6 months	Reduction in BPRS, SANS and SAPS. Brahmyadi yoga can be used as safe and effective add on.
9.	Sukanto Sarkar 2012	Case report	Single herb: *Brahmi* tablet 250 mg 1 BD Duration- 1 month	Add-on *Brahmi* to olanzapine in a case of paranoid schizophrenia resulted in improvement in psychopathologywithout any treatment emergent adverse effect.
10.	Kshama Gupta, Prasad Mamidi 2016	Case report (2 cases)	Purificatory procedure + polyherbal formulation: Ayurveda purificatory procedure + Palliative care Case 1–6 weeks, Case 2–8 weeks	Ayurvedic *panchakarma* procedures followed by polyherbal formulations resulted in symptom improvement in 'Undifferentiated type of schizophrenia'
11.	K N Roy Chengappa et al., 2018	Randomized double-blind Placebo controlled study n = 66 (trial-33, control-33)	Single drug extract: WSE extract 1000 mg/day Duration-12 weeks	A standardized extract of *Withania somnifera* when added adjunctively provides benefits for negative, general psychopathology, total symptoms and stress.
12.	Jessica M. Gannon et al., 2019	Randomized, placebo-controlled clinical trial n = 66 (trial-33, control-33)	Single drug extract: WSE extract 1000 mg/day Duration-12 weeks	*Withania somnifera* extract showed significant improvement in anxiety-depression symptoms in schizophrenia compared to control group.

their methodology. Only two of the twelve were randomized control trials with double-blinding, whereas eight other studies were not clear in their methodology. Further, few studies have used Ayurveda medications as an add-on therapy, while some have used as a standalone therapy contributing to the inhomogeneity in the methodology. As the protocols employed in these studies are diverse, we have categorized and discussed them based on the treatment composition i.e., single herbs, polyherbal formulations, bio-purificatory procedures and external therapies. We have also made an attempt at discussing the probable mechanism of action of these drugs that could have contributed to the symptom improvement in psychosis.

4.1. Single drugs/herbs

4.1.1. Brahmi

Brahmi as an add-on to olanzapine has shown better efficacy, significant improvement in psychopathology was seen after one month. *Brahmi* is extensively used in Ayurveda practice either independently or in combination with other herbs in various mental health conditions. Preclinical trials have demonstrated the antioxidant properties of *Brahmi* extracts on the brain, which could potentially lead to its positive effect on mental function [25]. It has been reported to enhance kinase activity, restore synaptic activity, ultimately enhancing neural transmission in the brain thus

repairing damaged neurons. Being a nootropic, its nootropic properties have been reported to be possibly mediated by its constituent saponins, bacosides A and B through glutamatergic mechanism [26]. Improvement in positive symptoms and general psychopathology in schizophrenia could possibly be mediated through the dopaminergic mechanism and its neurotransmission enhancing properties.

4.1.2. Ashwagandha

Ashwagandha extract (WSE) has reduced symptom exacerbation, anxiety, and depression in schizophrenia patients in two randomized controlled trials. Previous pre-clinical and clinical trials have confirmed potent anti-inflammatory, immunomodulating, and antioxidant properties of WSE [23]. In addition, WSE has also shown beneficial effects for anxiety, stress, and depression in separate clinical trials. WSE may restore the disturbed immune-inflammatory homeostasis and poor antioxidant defences repairing dysfunctional neural circuits and alterations in neurotransmitters associated with depression and anxiety symptoms in schizophrenia [27].

4.1.3. Tagara

Tagara (*Veleriana wallichii*) has also been shown to improve schizophrenia symptoms when compared to placebo but it was not statistically significant. The sedative effect of valerian is proven by previous clinical trials. Valepotriates are potent chemical constituents present in valerian responsible for this action [28]. Animal experiments had proven the antioxidant and neuroprotective properties of the drug [29]. Hence *Tagara* as a single drug or in combination with other herbs may contribute to improving psychotic symptoms.

4.2. Polyherbal formulations

Clinical trials on *B. yoga* containing powders of *Brahmi* (*Bacopa monnieri*), *Vacha* (*Acorus calamus*), *Sarpagandha* (*Rawolfia serpentina*), *Kushta* (*Saussurea lappa*), *Tagara* (*Valeriana wallichii*) and *Jatamamsi* (*Nardostachys jatamamsi*) have shown encouraging results in schizophrenia. *B. yoga* is hypothesized to break down pathogenesis of *Unmada* (schizophrenia) by clearing the "*manovaha srotas*" (channels of mind). The targets are the deranged *mana* (mind), *buddhi* (intellect), and other constituents of cognition [10]. Experimental trials suggest ethanolic extract of the roots of *Jatamansi* decrease the dopamine levels in the frontal cortical regions of the brain producing antipsychotic effects [30]. *Saussurea lappa* showed a protective effect on the brain by reducing oxidative stress in mice [31]. A preclinical study showed α-asarone of *A. calamus* exhibiting anti dopaminergic activity thereby showing antipsychotic effects [32]. *Sarpagandha* (*Rauwolfia serpentina*), is used in traditional system of medicine for the management of psychiatric disorders. Serpentine, extracted from *Sarpagandha* is a type II topoisomerase inhibitor which exhibits antipsychotic properties. Deserpidine is an ester alkaloid isolated from Rauwolfia also possesses antipsychotic action [33].

A study with Compound formulation containing *Shankhapushpi* (Convolvulus pleuricaulis), *Jatamamsi* (*Nardostachys jatamamsi*) *Brahmi* (*Bacopa monieri*), *Ashwagandha* (*W. somnifera*) and *Vacha* (*A. calamus*) reduced psychotic symptoms. Mode of action of these herbs when used in combination is not very clearly understood. However, the role of each drug in psychosis have been evaluated individually. Preclinical studies have shown anti stress, nootropic and neuroprotective activity of Convolvulus [34,35]. All other herbs in the compound are proven to be efficacious in psychosis in distinct studies [25,27,30,32]. Compound formulations may be expected to have equivalent or greater effect on psychotic symptoms. Another indigenous compound formulation GK022 containing *Shankhapushpi* (*Convolvulus pleuricaulis*), *Brahmi* (*Bacopa monieri*), *Ashwagandha* (*W. somnifera*), *Vacha* (*A. calamus*), *Sarpagandha* (*Rawolfia serpentina*), *Kushta* (*Saussurea lappa*), *Yahstimadhu* (*Glycyrrhiza glabra*), *Jatiphala* (*Myristica fragrance*) and *Chandrodaya rasa* (*Suvarna makaradhwaja*) was efficacious in schizophrenia. *Yashtimadhu* is one among the *medhya rasayana* (nootropic drug) [36]. Experimental trials have shown antidepressant like and memory enhancing effects of *Yashtimadhu* [37,38]. Extract of *Myristica fragrans* (nutmeg) has showed various behavioural effects in mice [39]. *C. rasa* or *S. makaradhwaja* is a poly-mineral drug made up of mercury, sulphur and gold [40]. Though specific indication of *C. rasa* in psychosis is not available, experimental study on mice has demonstrated substantial antioxidant property without any significant adverse effects [41].

Clinical trials on herbo-mineral compounds *S. sagara rasa* and *Unmada gaja kesari rasa* exhibited a significant reduction of psychopathology in cases of residual schizophrenia. Both of these formulations are indicated for *Unmada* in Ayurvedic classics [42]. *S. sagara rasa* showed improvements in paranoid and catatonic schizophrenia whereas there was a poor responses in hebephrenic and undifferentiated types. Patients of *kapha* and *vata* type of body constitution showed better response [18]. *S. sagara rasa* contains *Shuddha parada* (Purified and processed Mercury), *Shuddha gandhaka* (Purified and processed Sulphur), *Shuddha haratala* (Purified Orpiment - Arsenis tri sulphide), *Manashila* (Purified Realgar - Arsenic disulphide) and *Tamra bhasma* (calx of Copper) processed with decoction of *Vacha* (*A. calamus*), juice of *Brahmi* (*B. monnieri*) and oil prepared out of *Jyotishmati* (celestrus paniculatus). Though the action of these minerals on psychosis is not much explored, an experimental study on *Manashila* indicated sedative and hypnotic activity in animals [43]. Further, the drugs used for processing have been proven to have action on the brain. Especially, the seed oil of *Jyotishmati* is known for "*medhya*" (intellect promoting/nootropic) and potent antioxidant action [44].

Unmada gaja kesari rasa was more efficacious when used as add-on with conventional treatment. *Unmada gaja kesari rasa* has purified and processed *Parada*, *Gandhaka*, *Manashila*, *Dhattura* (seeds of Dhatura metel). It has been shown to be effective in *Kapha* predominant *Unmada* [45]. The aforesaid minerals are processed in juices of *Vacha* (*A. calamus*) and *Brahmi* (*B. monnieri*) which have a proven therapeutic efficacy in psychosis.

Kalyanaka ghrita, *Panchagavya* and *Mahapanchagavya ghrita* are classical preparations indicated in *Unmada*. Action of these formulations on central nervous system are proven by few preclinical as well as clinical trials. Ghee is considered as best among *snigdha dravya* (unctuous substances) which can be consumed daily. It alleviates *Vata* and *Pitta* without provoking *Kapha*. Classics suggest the role of ghee in enhancing cognition [46,47]. An experimental trial by Karandikar Y et al. suggests the role of ghee in improving learning and memory, in turn enhancing the cognition [48]. Cow's ghee is rich in polyunsaturated fatty acids (PUFA), omega 3 fatty acid and docosahexaenoic acid (DHA), linolenic acid. Studies suggest beneficial role of omega 3 fatty acid and DHA, and PUFA in various psychiatric disorders including schizophrenia [49].

Saraswtharishta and *Ashwagandharishta* are also used in few clinical trials on *Unmada*. Both the formulations are indicated in psychiatric disorders in classical texts. *Saraswtharishta* has shown potential neuroprotective and antidepressant effects in animal models [50,51]. With *Ashwagandha* (*Withania Somnifera*) as a main ingredient, *Ashwandharishta* has significant effect on psychosis as evidenced by separate clinical trials. Animal experimental studies indicate antioxidant property in *Ashwagandharishta* [52].

4.3. Purificatory procedures and external therapies

External therapies like *Udhwartana* (powder massage) with *Kolakulattha churna* have been tried in a case study with encouraging results. *Udhwartana* aims at pacifying and clearing the aggravated *kapha dosha* which has caused "*avarana*" to *vata* (impedance to functions of *vata*). Nose is said to be the gateway of the head according to Ayurveda [53]. Ayurveda hypothesizes that the medicines instilled through the nose get absorbed through the nasal mucosa and alleviate the disorders of the head and neck [54]. Nasal instillation with oil/ghee possessing cleansing property clears the *manovaha srotas* (channels of the mind) and help in alleviating the symptoms. "*Virechana*" (therapeutic purgation) aids removal of morbid *dosha* (vitiated bodily humors) through rectal route thereby leading to a reduction in symptoms. The mode of action of *Virechana* in systemic disorders is validated in various studies [55–57] but its mechanism of action in psychosis needs much more clarification through future clinical trials. The pharmacological properties of the drugs used for *Virechana* may also contribute to the efficacy of treatment.

"*Shirotalam*" is another procedure where powder of herbal drugs is applied over the vertex if the patient has restlessness, insomnia, and aggressiveness. Powders of herbs like *Amalaki* (*Phyllanthus emblica*), *Kushta* (*Suassurea lappa*) *Karpoora* (*Cinnamomum camphora*) and *Usheera* (*Vetivera zizinoides*) etc. are used for *Shirotalam* in Schizophrenia. This treatment may have local and systemic effects. According to Ayurveda, *shirotalam* pacifies the vitiated *prana vata*, *sadhaka pitta*, *tarpaka kapha* (different forms of bodily humors) and thereby reduces the symptoms [58]. The application of medicines on the head region has shown a calming-relaxing effect and improved stress response by enhancing circulation [59].

Stand-alone Ayurveda single drug therapy has limited application in cases of acute psychosis. Ayurveda treatment protocol comprising of judicious application of herbs, herbomineral compounds followed by panchakarma procedures showed better results in the management of psychotic disorders. Besides, efficacy of conventional treatment can be improved with addition of *Ashwagandha*, *Brahmi*, *Kalyanaka ghrita* or *Brahmi ghrita*. Apart from several single herbs there are also formulations indicated in psychotic disorders mentioned in classical texts such as *Lashunadya ghrita*, *Panchagavya ghrita*, *Kushmanda ghrita* etc which can be explored. All these treatments need to be evaluated in terms of mechanism of action by the application of various neurophysiological techniques.

5. Limitations

Although there are few RCTs exploring Ayurveda therapies in psychosis, the management across studies has not been uniform. The majority of these trials have been published almost two decades ago and have used different treatment regimens, including the drug, its dosage and duration of treatment. Very few studies have used single herbs. Some of the studies have judiciously utilized polyherbal formulations along with conventional treatment. Few studies have combined treatment protocols including several formulations and treatment procedures. Hence it was difficult to establish the action of individual drugs. Randomization, study design, and methods were not clearly mentioned in majority of the trials. The rationale for selection of drugs and mode of action in psychosis were not sufficiently discussed in these studies. Outcome measures were only limited to subjective criteria in some of the studies. In a few older studies, assessment scales used were not validated and conclusions were based on short term observations. Discussions in most of the studies are not satisfactory due to incomplete information on specific observations made during the study, method of blinding, follow up visits, and dropouts.

6. Conclusion

Role of Ayurveda, in the treatment of psychotic disorders is least explored. Currently available studies on the effect of Ayurveda treatment on psychotic disorders are very less in number to draw a valuable conclusion. Few clinical trials, pilot studies, and case reports are available but there is a lack of systematic randomized control trials and objective measures evaluating the mechanism of action of these treatments. Hence there is a large scope for conducting neurobiologically informed clinical research in the management of schizophrenia using Ayurveda approaches. This can help us in formulating neurobiologically informed, standardized protocols of integrative approach to the disease and provide better outcomes in the management of psychotic disorders including schizophrenia.

Grant support or other sources of funding

Authors acknowledge the funding received from the Ministry of AYUSH, Govt. of India under the AYURSWASTHYA Yojana. Scheme code: 3988 and Central Council for Research in Ayurvedic Sciences. VS acknowledges the support of the Wellcome Trust-DBT India Alliance Early Career Fellowship grant (IA/CPHE/18/1/503956). SV acknowledges Wellcome Trust-DBT India Alliance Intermediate Career Fellowship grant IA/CPHI/15/1/502026.

Author contributions

VS, UC, SV, and KKR were involved in the conceptualization of the study. Authors KK, VS, UC & HB managed the literature search and wrote the first draft of manuscript. All authors revised and optimized further versions of the manuscript. All the authors have contributed to and have approved the final manuscript.

Declaration of competing interest

None.

Acknowledgments

Authors acknowledge the funding received from Central Council for Research in Ayurvedic Sciences, Ministry of AYUSH, Govt. of India under the AYURSWASTHYA Yojana. Scheme code: 3988 VS acknowledges the support of the Wellcome Trust-DBT India Alliance Early Career Fellowship grant (IA/CPHE/18/1/503956). SV acknowledges Wellcome Trust-DBT India Alliance Intermediate Career Fellowship grant IA/CPHI/15/1/502026.

References

[1] Arciniegas DB. 3 behavioral neurology and neuropsychiatry. Psychosis. Continuum (Minneap Minn) 2015 Jun;21:715–36. https://doi.org/10.1212/01.CON.0000466662.89908.e7.

[2] Jongsma HE, Turner C, Kirkbride JB, Jones PB. International incidence of psychotic disorders, 2002–17: a systematic review and meta-analysis. Lancet Public Health 2019 May 1;4(5):e229–44. https://doi.org/10.1016/S2468-2667(19)30056-8.

[3] Moreno-Küstner B, Martín C, Pastor L. Prevalence of psychotic disorders and its association with methodological issues. A systematic review and meta-analyses. PLoS One 2018;13(4):e0195687. https://doi.org/10.1371/journal.pone.0195687. Published 2018 Apr 12.

[4] McGrath J, Saha S, Chant D, Welham J. Schizophrenia: a concise overview of incidence, prevalence, and mortality. Epidemiol Rev 2008;30:67–76. https://doi.org/10.1093/epirev/mxn001.

[5] Rössler W, Salize HJ, van Os J, Riecher-Rössler A. Size of burden of schizophrenia and psychotic disorders. Eur Neuropsychopharmacol 2005 Aug;15(4):399–409. https://doi.org/10.1016/j.euroneuro.2005.04.009.
[6] Hoenders HJR, Bartels-Velthuis AA, Vollbehr NK, Bruggeman R, Knegtering H, de Jong JTVM. Natural medicines for psychotic disorders: a systematic review. J Nerv Ment Dis 2018 Feb;206(2):81–101. https://doi.org/10.1097/NMD.0000000000000782.
[7] van Os J, Kapur S. Schizophrenia. Lancet. 2009 Aug 22;374(9690):635–45. https://doi.org/10.1016/S0140-6736(09)60995-8.
[8] Haddad PM, Brain C, Scott J. Nonadherence with antipsychotic medication in schizophrenia: challenges and management strategies. Patient Relat Outcome Meas 2014 Jun 23;5:43–62. https://doi.org/10.2147/PROM.S42735.
[9] Hazra M, Noh S, Boon H, Taylor A, Moss K, Mamo D. Complementary and alternative medicine in psychotic disorders. J Compl Integr Med 2010 Jan 4:7.
[10] Sharma RK, Dash B, editors. Commentary dipika of chakradatta on Charaka Samhita of Charaka, chikitsa sthana; unmada chikitsa: chapter 9, verse 5. reprint ed. Varanasi: Chaukhamba Sanskrit Series; 2019. p. 410.
[11] Sharma S, Dash B, editors. Commentary dipika of chakradatta on Charaka Samhita of Charaka, nidana sthana; unmada nidana: chapter 7, verse 5. reprint ed. Varanasi: Chaukhamba Sanskrit Series; 2019. p. 89.
[12] Sharma RK, Dash B, editors. Commentary dipika of chakradatta on Charaka Samhita of Charaka, chikitsa sthana; unmada chikitsa: chapter 9, verse 25-28. reprint ed. Varanasi: Chaukhamba Sanskrit Series; 2019. p. 421–2.
[13] Mahal AS, Ramu NG, Chaturvedi DD. Double blind controlled study of brahmyadiyoga and tagara in the management of various types of unmada (schizophrenia). Indian J Psychiatr 1976;18(4):283–92.
[14] Ramu MG, Senapati HM, Janakiramaiah N, Shankara MR, Chaturvedi DD, Murthy NSN. A pilot study of role of brahmyadiyoga in chronic unmada(-schizophrenia). Ancient Sci Life 1983;2(4):205–7. PMCID: PMC3336759.
[15] Dash SC, Tripathi SN, Singh RH. Clinical assessment of medhya drugs in the management of psychosis (unmada). Ancient Sci Life 1983;3(2):77–81. PMCID: PMC3331543.
[16] Parikh MD, Pradhan PV, Shah LP, Bagadia VN. Evaluation of indigenous psychotropic drugs - a preliminary study. J Research Ayurveda Siddha 1984;5(1–4):12–7.
[17] Ramu MG, Venkataram BS. A controlled study of ayurvedic treatment in the acutely ill patients with schizophrenia (unmada) - rationale and results. NIMHANS Journal, [S.l] 1992:1–16.
[18] Tripathi JS, Singh RH. Clinical evaluation of smrtisagararasa in cases of residual schizophrenia. J Research Ayurveda Siddha 1994;15(1–2):8–16.
[19] Chaudhari Onkar, Gupta S, Singh RH. Evaluation on an ayurvedic formulation for the management of residual schizophrenia. J Research Ayurveda Siddha 2003;24(1–2):51–61.
[20] Rao BCS, Tiwari SK, Sahoo S, Ramana GV, Gupta HK, Sudhakar D. Efficacy of Brahmyadi yoga in the management of unmada (schizopharenia). Aryavaidyan 2011;24(23):145–52.
[21] Sarkar S, Mishra BR, Praharaj SK, Nizamie SH. Add-on effect of brahmi in the management of schizophrenia. J Ayurveda Integr Med 2012;3(4):223–5. https://doi.org/10.4103/0975-9476.104448.
[22] Gupta K, Mamidi P. Case study ayurvedic management of schizophrenia: report of two cases. Int Res J Pharm 2016 Oct 12;2016:41–4.
[23] Chengappa KNR, Brar JS, Gannon JM, Schlicht PJ. Adjunctive use of a standardized extract of withania somnifera (Ashwagandha) to treat symptom exacerbation in schizophrenia: a randomized, double-blind, placebo-controlled study. J Clin Psychiatry 2018 Jul 10;79(5). https://doi.org/10.4088/JCP.17m11826.
[24] Gannon J, Brar J, Rai A, Chengappa K. Effects of a standardized extract of Withania somnifera (Ashwagandha) on depression and anxiety symptoms in persons with schizophrenia participating in a randomized, placebo-controlled clinical trial. Ann Clin Psychiatr 2019 May 1;31:123–9.
[25] Aguiar S, Borowski T. Neuropharmacological review of the nootropic herb bacopa monnieri. Rejuvenation Res 2013 Aug;16(4):313–26. https://doi.org/10.1089/rej.2013.1431.
[26] Mathur D, Goyal K, Koul V, Anand A. The molecular links of Re-emerging therapy: a review of evidence of Brahmi (bacopa monniera). Front Pharmacol 2016 Mar 4;7:44. https://doi.org/10.3389/fphar.2016.00044.
[27] Chengappa KN, Bowie CR, Schlicht PJ, Fleet D, Brar JS, Jindal R. Randomized placebo-controlled adjunctive study of an extract of withania somnifera for cognitive dysfunction in bipolar disorder. J Clin Psychiatry 2013;74(11):1076–83. https://doi.org/10.4088/JCP.13m08413.
[28] Toolika E, Bhat NP, Shetty SK. A comparative clinical study on the effect of Tagara (Valeriana wallichii DC.) and Jatamansi (Nardostachys jatamansi DC.) in the management of Anidra (primary insomnia). Ayu 2015;36(1):46–9. https://doi.org/10.4103/0974-8520.169008.
[29] Ayyathan DM, Chandrasekaran R, Thiagarajan K. Neuroprotective effect of Tagara, an Ayurvedic drug against methyl mercury induced oxidative stress using rat brain mitochondrial fractions. BMC Compl Alternative Med 2015;15:268. https://doi.org/10.1186/s12906-015-0793-2. Published 2015 Aug 12.
[30] Jash R, Choudary KA, Prasanth DSNBK. Evaluation of antipsychotic activity of ethanolic extract of Nardostachys jatamansi on Wistar albino rat. Int J Pharma Sci Res 2013;4(7):2730–6.
[31] Abdel-Rahman M, Rezk MM, Ahmed-Farid OA, Essam S, Abdel Moneim AE. Saussurea lappa root extract ameliorates the hazards effect of thorium induced oxidative stress and neuroendocrine alterations in adult male rats. Environ Sci Pollut Res 2020 Apr 1;27(12):13237–46. https://doi.org/10.1007/s11356-020-07917-y.
[32] Pandy V. Antipsychotic-like activity of α-asarone in mice: a preliminary report. APCT [Internet] 2016;1(1). https://doi.org/10.23880/APCT-16000106 [cited 2020 Sep 26].
[33] Kumari R, Rathi B, Rani A, Tiwari SM, Bhatnagar S, Rauvolfia serpentina L, et al. Phytochemical, pharmacological and therapeutic aspects. Int J Pharmaceut Sci Rev Res 2013 Jan 1;23:348–55.
[34] Das R, Sengupta T, Roy S, Chattarji S, Ray J. Convolvulus pluricaulis extract can modulate synaptic plasticity in rat brain hippocampus. Neuroreport 2020 May 22;31(8):597–604.
[35] Shalavadi MH, Chandrashekhar VM, Muchchandi IS. Neuroprotective effect of Convolvulus pluricaulis Choisy in oxidative stress model of cerebral ischemia reperfusion injury and assessment of MAP2 in rats. J Ethnopharmacol 2020;249:112393. https://doi.org/10.1016/j.jep.2019.112393.
[36] Sharma RK, Dash B, editors. Commentary dipika of chakradatta on Charaka Samhita of Charaka, chikitsa sthana; rasayana chikitsa: chapter 1/3, verse 30-31. reprint ed. Varanasi: Chaukhamba Sanskrit Series; 2019. p. 46.
[37] Dhingra D, Sharma A. Antidepressant-like activity of Glycyrrhiza glabra L. in mouse models of immobility tests. Prog Neuro-Psychopharmacol Biol Psychiatry 2006 May;30(3):449–54. https://doi.org/10.1016/j.pnpbp.2005.11.019.
[38] Dhingra D, Parle M, Kulkarni SK. Memory enhancing activity of Glycyrrhiza glabra in mice. J Ethnopharmacol 2004 Apr;91(2–3):361–5. https://doi.org/10.1016/j.jep.2004.01.016.
[39] Jaiswal P, Kumar P, Singh V, Singh D. Biological effects of Myristica fragrans. Annual Review of Biomedical Sciences 2009 Mar 4:11. https://doi.org/10.5016/1806-8774.2009v11p21.
[40] Khedekar S, Prajapati P, Ruknuddin G, Patgiri B. A scientific review of gold containing herbo-mineral preparation: makaradhwaja. Int J Green Pharm 2015 Oct 1;9:7–11.
[41] Sinyorita S, Ghosh CK, Chakrabarti A, Auddy B, Ghosh R, Debnath PK. Effect of Ayurvedic mercury preparation Makaradhwaja on geriatric canine–a preliminary study. Indian J Exp Biol 2011 Jul;49(7):534–9.
[42] Das G. Bhaishhjya ratnavali. In: Mishra BB, editor. Vidyotini" Hindi commentary analysis with appendixes by shri kaviraj ambikadatta shastri. 18th ed. Varanasi: Chaukhamba Sanskrit Bhavan; 2005. p. 514.
[43] Kodlady N, Doddamani MS, Vishwanath Y, Patgiri BJ. Sedative hypnotic activity of manahshila (realgar) -an experimental evaluation. Ancient Sci Life 2011;30(3):78–83. PMID: 22557432.
[44] Arif PT, Shaligram SS, Babasaheb KS. Pharmacological profile of Jyotishmati (Celastrus paniculatus willd): a review. Int J Ayu 2018 Sep 30;7(3):66–89.
[45] Dubey S, Tripathi JS, Gupta S, Reddy KR. A Comparative clinical trial on the role of Panchakarma therapy and Unmada Gajankusha Rasa in the cases of major depressive disorder vis-à-vis kaphaja Unmada. Ayu 2010;31(2):205–9. https://doi.org/10.4103/0974-8520.72396.
[46] Sharma RK, Dash B, editors. Commentary dipika of chakradatta on Charaka Samhita of Charaka, sutra sthana; annapanavidhi: chapter 27, verse 231-232. reprint ed. Varanasi: Chaukhamba Sanskrit Series; 2019. p. 537.
[47] Paradkar BH, editor. Sarvanga sundara commentary of arunadatta and Ayurveda rasayana commentary of hemadri, sootra sthana. reprint ed. New Delhi: Rashtriya Sanskrit Samsthana; 2002. p. 73–4 [Chapter 5], Verse 37-39.
[48] Karandikar YS, Bansude AS, Angadi EA. Comparison between the effect of cow ghee and butter on memory and lipid profile of wistar rats. J Clin Diagn Res 2016 Sep;10(9):FF11–5. https://doi.org/10.7860/JCDR/2016/19457.8512.
[49] Joshi KS. Docosahexaenoic acid content is significantly higher in ghrita prepared by traditional Ayurvedic method. J Ayurveda Integr Med 2014;5(2):85–8. https://doi.org/10.4103/0975-9476.131730.
[50] Parekar RR, Jadhav KS, Marathe PA, Rege NN. Effect of Saraswatarishta in animal models of behavior despair. J Ayurveda Integr Med 2014;5(3):141–7. https://doi.org/10.4103/0975-9476.140469.
[51] Prabhu J, Prabhu K, Chaudhuri A, Rao MR, Selvi VS, Balaji TK, et al. Neuroprotective effect of Ayurveda formulation, saraswatharishtam, on scopolamine induced memory impairment in animal model. Phcog J 2020;12(1):6–13. https://doi.org/10.5530/pj.2020.12.2.
[52] Tiwari Preeti, Patel Rakesh K. Estimation of total phenolics and flavonoids and antioxidant potential of Ashwagandharishta prepared by traditional and modern methods. Asian J. Pharm. Ana. Oct. - Dec. 2013;3(4):147–52.
[53] Paradkar BH, editor. Sarvanga sundara commentary of arunadatta and Ayurveda rasayana commentary of hemadri, sootra sthana; nasyavidhi adhayaya : chapter 20, verse 5. reprint ed. Varanasi: Chowkhambha Sanskrit Series; 2006. p. 287.
[54] Ramteke RS, Patil PD, Thakar AB. Efficacy of Nasya (nasal medication) in coma: a case study. Ancient Sci Life 2016;35(4):232–5. https://doi.org/10.4103/0257-7941.188188.
[55] Chaturvedi A, Rao P, Kumar M, Ravishankar B, Rao N, Mundugaru R. Effect and mechanism of virechana karma (therapeutic purgation) over fructose-induced metabolic syndrome: an experimental study. J Evid Based Complementary Altern Med 2015 Jul 22:21. https://doi.org/10.1177/2156587215596283.

[56] Kaur M, Chandola H. Role of virechana karma in cure and prevention of recurrence of vicharchika (eczema). Ayu 2012;33(4):505–10. https://doi.org/10.4103/0974-8520.110526.
[57] Suma DS, Shridhara BS. Mode of action of virechana in migraine - a conceptual study, IJAR - Indian Journal of Applied Research| World Wide Journals [Internet]. [cited 2021 Jan 30] 2018;8(7):30–1.
[58] Gupta Arun kumar, Gupta Trupti. Standard operative procedure & probable mode of action shiropichu. wjpmr 2020 Jan;6(10):291–3.
[59] Dhuri KD, Bodhe PV, Vaidya AB. Shirodhara: a psycho-physiological profile in healthy volunteers. J Ayurveda Integr Med 2013;4(1):40–4. https://doi.org/10.4103/0975-9476.109550.