JAASP http://www.aaspjournal.org
Journal of Asian Association of Schools of Pharmacy 2019; 8: 22–49

Review

Effect of herbal and nutritional products on the central nervous system effects of haloperidol: a systematic review

Rosina Yau Mok[1], Sophia Yui Kau Fong[1], Mengbi Yang[1], Tonia Hoi-Tung Sung[2], Yin Cheong Wong[1], Tianjing Ren[1], Cheuk Hin Chow[1], Qiong Gao[1] and Zhong Zuo[1,*]

[1] School of Pharmacy, Faculty of Medicine, The Chinese University of Hong Kong, Shatin, New Territories, Hong Kong SAR
[2] Leslie Dan Faculty of Pharmacy, University of Toronto

Received March 20, 2019
Revised May 8, 2019
Revised June 6, 2019
Accepted June 9, 2019

* Corresponding author
School of Pharmacy, The Chinese University of Hong Kong, Shatin, N.T., Hong Kong SAR
E-mail: joanzuo@cuhk.edu.hk

ABSTRACT

Haloperidol is widely used in treatments of acute and chronic schizophrenia. Due to the narrow therapeutic window of haloperidol and the increasing popularity of herbal and nutritional products (HNPs), it is important to have comprehensive understanding on the interactions between haloperidol and HNPs. The current review is the first to provide systematic evidences from both animal and clinical studies on haloperidol-HNPs interactions. Due to the diversity of the reviewed studies, quantitative meta-analysis is not possible. Two major outcomes of haloperidol-HNPs interactions include the changes in level of catalepsy and in level of extrapyramidal side-effects. The mechanisms of these interactions remain unclear, yet factors such as modulations on oxidative stress and dopaminergic pathway were proposed. Only nine clinical trials were identified, indicating further exploration on the clinical utilization of haloperidol with HNPs is warranted. Based on the results of the current review, it is advised to monitor the potential risk of interactions between haloperidol and co-administrated HNPs in clinical practice.

Key words: haloperidol, herb and nutritional products, herb-drug interactions, catalepsy, extrapyramidal side-effects, antipsychotics

1. Background

As a part of complementary and alternative medicine, herbal and nutritional products (HNPs) are widely used around the world with escalating prevalence throughout decades (Izzo and Ernst, 2001; Kuhn, 2002; MacLennan et al., 2002; Zhang et al., 2011). They have also received increasing attention in the management of chronical conditions such as psychiatric disorders (Beaubrun and Gray, 2000; Csernansky and Schuchart, 2002; Matthews et al., 2003; Zhang et al., 2010). A survey by Grzywaczs et al. demonstrated that herbal and nutritional compounds are widely used among older adults with depression or anxiety, with a rate as high as of 82% (Grzywacz et al., 2006). In addition, the prevalence of concomitant use of Chinese medicine and antipsychotics in schizophrenic patients was reported to be around 36.4% (Zhang et al., 2011). Although the prevalence of co-administration of HNP with drugs in CNS patients is high, it is reported that 61.5% of adults in the US that was taking at least one herbal compound had not consulted or disclosed such use to their physicians (Fugh-Berman, 2000). Such lack of guidance from healthcare professionals together with under-researched safety information of the HNPs bring out the safety concern of HNPs in combination with therapeutic drugs in psychiatric treatments (Cocka, 2015; Ernst, 1998).

As one of the first-generation antipsychotics, haloperidol was introduced in 1958 and has been widely used in western countries (Granger and Albu, 2005). This butyrophenone antipsychotic is most commonly used in treatments for both acute and chronic schizophrenia, as well as mania, autism in children, Gilles de la Tourette's syndrome, *etc* (Kane et al., 2002; McIntyre et al., 2005; Perry et al., 1989; Shapiro et al., 1989; Wyosky and Baum, 1989) via intravenouse, intramuscular or oral administrations. Due to its narrow therapeutic window and large inter-individual variability of pharmacokinetics, clinical drug monitoring of haloperidol is recommended (Kudo and Ishizaki, 1999; Ulrich et al., 1998). Haloperidol is extensively metabolised in the liver with CYP3A4 and CYP2D6 being the principle enzymes (Fang et al., 1997). Glucuronidation is also reported to play a major role in haloperidol metabolism (Someya et al., 1992). The

blockade of dopamine receptors, specifically the D2 receptors family, was considered central to antipsychotic activity of haloperidol (Kapur and Mamo, 2003; Kapur and Remington, 2001; Saeedi et al., 2006). Such properties make it prone to interact with co-administered substances including HNP. Moreover, the antagonism of such receptors is also considered a major cause of the extrapyramidal side-effects (EPS) and therefore limits the clinical utilities of antipsychotics (Reynolds, 2004). Chronic administration of haloperidol can also induce motor dysfunction, including tardive dyskinesia (Beasley et al., 1999).

Research publications, especially review articles, are considered one of the major information resources for healthcare professionals when they are making clinical decisions regarding usage of herbal or dietary supplements (Howard et al., 2001). Although there are a few review articles on interactions between antipsychotic treatments and HNPs (Knable, 2002; Rathbone et al., 2005; Rathbone et al., 2007; Singh et al., 2010), they barely cover the details of haloperidol, suggesting that there is an evidence gap in terms of comprehensive reviews on the interactions between HNP and haloperidol. By taking a systematic approach, the current review has summarized the existing scientific evidence on interactions between haloperidol and HNPs. Studies that demonstrated information from animal models and clinical trials were identified and the potential mechanism behind it was explored, aiming to provide a more comprehensive guidance for the healthcare professionals.

2. Methodology

2.1. Literature Search

Electronic computer-based search was made using the following databases: EMBASE (1980–Jan. 2019), EMBASE Classic (1947–1979), MEDLINE (1966–Jan. 2019), OLDMEDLINE (1946–1965), PubMed (1946–Jan. 2019), Allied & Complementary Medicine (AMED) database from the Health Care Information Service of the British Library (1985–Jan. 2019), Cochrane Library (1992–Jan. 2019), Cinahl Plus (1937–Jan. 2019), SciFinder Scholar (1907–Jan. 2019), Stockley's Herbal Medicines Interactions (1907–Jan. 2019) and Natural Medicines Comprehensive Databases (1985–Jan. 2019). Both the drug names and its brand names/ commonly used names were used as search terms of haloperidol ("Haloperidol", "R-1625", "Haldol", and "Serenace"). A comprehensive list of keywords and Medical Subject Headings (MeSH) search terms for herbs, food and dietary supplements which was previously developed were combined with the search terms of haloperidol (Table 1) (Fong et al., 2013; Fong et al., 2014).

2.2. Study Screening

Articles contained data involving interactions of HNPs with haloperidol are considered eligible for evaluation. The HNPs were categorized as "traditional Chinese medicine (TCM)", "food and dietary supplements" and "other herbal products". For the TCM category, Latin names for herbs were standardized as consulted to the official compendium Pharmacopoeia of the People's Republic of China 2015 (Chinese Pharmacopoeia) and/or Zhong Hua Ben Cao (Chinese Materia Medica). The term "food and dietary supplements" was defined by The Dietary Supplement Health and Education Act of 1994 (DSHEA). According to such act, "dietary supplement" refer to any dietary products (other than tobacco) containing one or more of the following dietary ingredients: vitamin, mineral, herb or other botanical, amino acid, a dietary substance for use by man to supplement the diet by increasing the total dietary intake. Any specific traditional food/fruit products or beverages were categorized as "food". Relevant reports were selected and validated for their eligibility by two reviewers (Fong and Mok) independently. Due to the limited availability of clinical information, all related clinical trials were included regardless of their study characteristics. Articles on in-vivo animal studies or on clinical trials were included if they contained data involving interactions of haloperidol with TCM, herbs, food and dietary supplements. Exclusion criteria were as follows: (1) full text not available, (2) non-English language articles, (3) review and meta-analysis articles, (4) other irrelevant studies such as in-vitro studies, case reports, etc.

2.3. Quality Assessment

Clinical trials were assessed by two reviewers independently for methodological quality using the revised Cochrane risk of bias tool from the following five domains: (1) bias arising from the randomization process, (2) bias due to deviations from intended interventions, (3) bias due to missing outcome data, (4) bias in measurement of the outcome, (5) bias in selection of the reported result. A rating was given for each trial based on the three quality categories (Higgins et al., 2011). In addition, the Jadad Scale (Jadad et al., 1996) was also applied for quality assessment on clinical trials by two independent reviewers, measuring factors that impact on the quality of a trial including: (1) randomization, (2) double-blinding and (3) description on withdrawals and drop outs. A rating scale from 0 to 5 was given for each trial based on the three aspects.

2.4. Data Synthesis

The current article is a systematic review on different types of herb-drug interaction studies without meta-analysis, due to the variety of the study designs and the diversity of the clinical and pre-clinical outcomes, quantitative data synthesis is not possible, and descriptive data synthesis is conducted to summarize the pharmacokinetic and pharmacodynamic interaction between HNPs and haloperidol. Review protocol of the current study was not registered. Supplementary Table 1 showed the PRISMA checklist of the current review.

Table 1. Keywords and MeSH search terms for herbs, food and dietary supplements.

Keywords	MeSH terms
(tradition* and chines* and medic*).mp.	exp Chinese drug
(drug* and chines* and herb*).mp. (TCM or CHM).tw.	exp Chinese medicine exp Chinese herb
(plant* and medic*).mp. traditional chinese.tw. (chinese adj (herb$ or drug$ or formul$ or plant$ or presri$ or remed$ or materia medica)).ab,ti,ot.	exp herbal medicine exp herbaceous agent exp plant extract
((herb$ or drug$ or formul$ or plant$ or presri$ or remed$ or materia medica) adj chinese).ab,ti,ot.	exp diet supplementation 1
herbal remed$.tw.	exp food drug interaction 9
(plant* and extract*).mp.	exp food 910
alter* medic*	exp Drugs, Chinese Herbal 17
integrative medicin$.ab,ti,ot.	exp Plant Extracts 61
(phytodrug$ or phyto-drug$ or phytopharmaceutical$).tw.	exp Plants, Medicinal 41
(herb or herbs or herbal).tw. Nutrition$ supplement or diet$ supplement.mp.	exp Medicine, Oriental Traditional exp Medicine, chinese traditional 6
	exp Phytotherapy 32 exp Medicine, Ayurvedic 3 exp Medicine, east asian traditional
	exp medicine, kampo exp medicine, korean traditional exp medicine, tibetan traditional
	exp medicine, mongolian traditional
	exp shamanism/

3. Results

3.1. Literature Search

A total of 1700 articles were found through the initial database searches and by scrutinizing the bibliographies of relevant literatures, within which 226 articles fulfilled the inclusion criteria and were selected for further evaluation. A final 155 articles were evaluated as eligible for full text extraction, including 145 original articles and 10 review articles. Such articles then underwent in-depth evaluations performed by 3 reviewers (Mok, Fong, Sung) independently. The current review has identified 9 clinical studies and 89 animal studies (Figure 1). The majority of studies are focusing on the haloperidol-induced catalepsy model (n = 44) and EPS related studies (n = 25). Articles exploring other outcome measure such as dopamine level, antipsychotic effect, sexual stimulating effect etc. were also included.

3.2. Risk of Bias

The risk of bias of the 9 clinical studies was evaluated by the revised Cochrane risk of bias tool, and the quality of the studies was evaluated by the Jadad scale (0–5). Among the 9 clinical studies, three studies received high Jadad scale of 4 and were categorized as low risk of bias, 1 double-blind controlled trial received Jadad scale of 3 with some concerns of bias, 1 open-label randomized study with Jadad scale of 3 and other 4 studies with low Jadad scales (equal or less than 2) were categorized as high risk of bias.

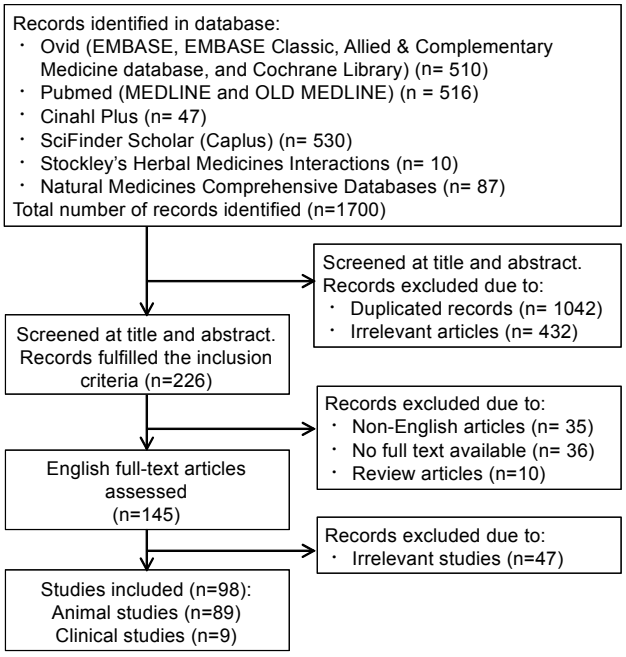

Figure 1. Study flow diagram.

The risk of bias of all animal studies were relatively high compared with the clinical trials. Although all studies properly presented baseline characteristics and outcomes, none of the studies reported on allocation concealment, random housing, blinding of the caregivers, or blinding and randomization of outcome assessment. All of the animal studies were parallel design, and available information on the type of animals used in the studies, dose and duration of haloperidol, types of outcomes, and timing of outcome measurements were all summarized in the Tables 2, 3 and 5.

3.3. Effect of Herbs on Haloperidol-Induced Catalepsy Model

A total of 41 HNPs were identified in 44 articles for potential interactive effect on the haloperidol-induced catalepsy model with the catalepsy score of the studied rodent being the main outcome measure. Out of the 44 articles, 15 articles investigated the effect of TCM on the model, 24 articles investigated on other herbal products and 5 articles on food and dietary supplements (Table 2).

Among the identified 41 HNPs, 8 HNPs reported to have no significant effect on the haloperidol-induced catalepsy, including Solanum nigrum Linn., Cassia sophera Linn., Ageratum conyzoides Linn., Momordica dioica, Phyllanthus maderaspatensis Linn., Pueraria tuberosa, Randia dumetorum and Ficus Bengalensis Bark (Ghaisas et al., 2008; Maharudra et al., 2011; Nagore et al., 2009; Nirmal et al., 2009; Nirmal et al., 2012; Rao et al., 2008; Taur et al., 2007; Tote et al., 2009). Although specific mechanisms were not documented, it was believed that these HNPs do not have activities on dopaminergic transmission and hence did not show significant effect on the animals in the haloperidol-induced catalepsy model.

Among the 33 HNPs reported to have activities on the model, 11 of them reported a potentiation effect. Among which, Morus alba Linn., Acorus calamus Linn., Piper betel, Hibiscus rosa-sinensis root are reported to possess the ability to decrease dopamine level in striatum and therefore showed significant potentiation of catalepsy (Ka et al., 2009; Nade et al., 2009; Vyawahare and Bodhankar, 2007; Yadav and Nade, 2008). The mechanism for Ginkgo biloba leaf extract (EGb 761) to increase haloperidol-induced catalepsy was not clear and requires further exploration (Fontana et al., 2005). Although the specific mechanism remains unknown, Alpha-tocopherol (Vitamin C) showed potentiation effect on both rats and monkeys by producing marginal effect on dopaminergic transmission while alpha-tocopherol (Vitamin E) might potentiate catalepsy on mice by inhibiting inducible protein kinase C activity in smooth muscle cells and completely preventing glutamate induced cell death without decreasing glutamate induced accumulation of intracellular peroxides (Lazzarini et al., 2005).

Besides the non-active and potentiating HNPs, a total of 22 HNPs are found to significantly decrease the catalepsy score. The suggested mechanisms include 1) acting as dopaminergic agonist agent or D2 receptor agonist (Boerhavia diffusa L., Nardostachys jatamansi, Trichilia catigua, anacyclus pyrethrum, Caffeine); 2) affecting dopamine level through increasing histamine level (Piper longum Linn., Anacardium occidentale L.); 3) demonstrating neuroprotective effect in stress-induced dopamine neuron degeneration (BR-16A, an herbal psychotropic preparation which contains: Bacopa monnieri, Centella asiatica, Acorus calamus, Withania somnifera, Tinospora cordifolia, Embelica officinalis, Evolvulus aisinoides, Saussurea lappa, Terminalia belerica, Terminalia chebula, Terminalia arjuna); 4) changing antioxidant enzymes level such as superoxide dismutase (SOD), glutathione peroxidase and catalase by quenching the free radicals to combat oxidative stress in brain tissue (Smilax zeylanica L., Withania somnifera, Emblica officinalis, Murraya koenigii, Alpha lipoic acid, Canscora decussate); 5) possessing CNS-depressant effect through the γ-aminobutyric acid type A (GABA-A) receptors (Bauhinia tomentosa L.) and 6) containing dopamine (mucuna pruriens). Other HNPs such as Hypericum perforatum, Rosmarimus officinalis., Triphala (An Ayurvedic herbal rasayana formula consisting of Hebulae Fructus, Terminaliae Belliricae Fructus and Phyllathus Emblica Officinalis), Smilax zeylanica L., and Carya illinoensis also showed significant protective effect against haloperidol-induced catalepsy, but specific mechanisms of such interactions were not discussed.

3.4. EPS Related Interaction

As one of the most commonly seen side-effects of antipsychotics, EPS include acute symptoms of dystonia, Parkinsonism, tardive dyskinesia (TD) and akathisia (Knable, 2002). Catalepsy tests in rodents including block test, horizontal bar test and inclined-grid test are commonly used models to evaluate the antipsychotic-induced acute parkinsonism (Fong et al., 2013). Mechanistic study has suggested that the brain mechanisms involved in the meditation of catalepsy in rats and EPS in humans might be similar. It is also reported that the behavioural deficits induced by acute administration of relatively low doses of haloperidol in rats are both analogous and homologous to the haloperidol-induced Parkinsonism symptoms in humans (Fong et al., 2014). These findings indicate that such preclinical models are feasible to assess the liability of haloperidol to induce EPS in humans. There are total 25 articles from animals (n = 16) and humans (n = 9) reported haloperidol associated EPS, among which 8 articles were on TCM, 6 articles on herbal products and 11 articles on food and dietary supplements.

In the reports from animal models (Table 3), activities including parkinsonism, locomotor activity and TD were commonly evaluated. Nardostachys jatamansi was reported to reverse haloperidol-induced Parkinsonism by up regulation of dopaminergic signalling and enhancing the

Table 2. Effect of HNPs on Haloperidol-induced Catalepsy (HIC) Animal Model.

Type	Product	Model	Outcomes and findings			Reference
			Measurement	Mechanism	Efficacy	
TCM	Nardostachys jatamansi	Adult Wistar rats	Catalepsy↓, peroxide level↑, antioxidant level↑	Oral administration of NJ along with haloperidol significantly restored the peroxides and antioxidant levels to near normal in the brains of the test animals.	Nardostachys jatamansi (NJ) was investigated for its anticataleptic effects in the HIC rat model. Rats (n = 6) received NJ at a dose of 100, 250, 500 mg/kg 30 min before haloperidol (1 mg/kg, i.p.) was administrated to induce catalepsy. Significant reversal in catalepsy was observed with the administration of NJ aqueous extract. The maximal decrease in catalepsy was observed in the group receiving aqueous extract of NJ at a dose of 250 mg/kg. No pronounced reduction in the cataleptic scores at a dose of 500 mg/kg.	(Rasheed et al., 2010)
TCM	Solanum nigrum L.	Male Swiss mice	Catalepsy△	N.D.	There was no significant reduction in the duration of HIC by the co-administration of S. nigrum berry extract (50, 100 and 200 mg/kg, i.p.). No other side effects of the concurrent administration of Haloperidol and S. Nigrum were mentioned.	(Nirmal et al., 2012)
TCM	Boerhavia diffusa L.	Adult albino rats	Catalepsy↓	The extract was acting similarly like agent which is dopaminergic agonist or working as D2 receptor agonist.	The result showed that the hydro-alcoholic extract of Boerhaavia diffusa of leaves at a dose 100 and 200 mg/kg by p.o significantly decreased the catalepsy induced by haloperidol.	(Gadekar and Jitender, 2011)
TCM	Piper longum L.	Albino mice	Catalepsy↓	N.D.	All P. longum fruit extracts at all concentrations significantly decreased the duration of HIC for each time interval. No other side effects of the concurrent administration of haloperidol and P. Longum were mentioned.	(Kaushik et al., 2012)
TCM	Anacardium occidentale L.	Mice	Catalepsy↓	N.D.	All concentrations of A. occidentale extract significantly decreased the duration of HIC. Maximum protection against HIC was observed at the A. Occidentale dose of 375 mg/kg. No other side effects of the concurrent administration of Haloperidol and A. Occidentale were mentioned.	(Mahajan et al., 2011)
TCM	Hypericum perforatum	Male Wistar rats	Catalepsy↓	N.D.	The comparative antidepressant activity of the extracts of Hypericum perforatum (20 mg/kg, p.o.) using HIC model in rats (n = 6) was evaluated. The result showed a significant protection against HIC compared to control at 30 min after injection of haloperidol. The study revealed the extracts of Hypericum perforatum might have a promising antidepressant potential.	(Moinuddin et al., 2011)
TCM	Rosmarimus officinalis	Male Wistar rats	Catalepsy↓	N.D.	The comparative antidepressant activity of the extracts of Rosmarimus officinalis (20 mg/kg, p.o.) using HIC model in rats (n = 6) was evaluated. The result showed a significant protection against HIC at 60 min after injection of haloperidol.	(Moinuddin et al., 2011)
TCM	Triphala [1]	Male albino mice	Catalepsy↓	N.D.	The protective effect of Triphala on HIC was studied in mice (n = 6). Catalepsy was induced with haloperidol (1 mg/kg), Triphala (2.5, 6.25 and 12.5 mg/kg, p.o.) was administered to three groups of mice respectively while the other groups received the vehicle (10 ml/kg). Single dose of the test drug and vehicle were used in the acute study, a significant decrease in the cataleptic score was observed at all time intervals except at the 30 min interval. In the chronic study, the single doses were given once a day for seven days with a significant decrease in the cataleptic score observed.	(Narita et al., 1982)

Table 2. Effect of HNPs on Haloperidol-induced Catalepsy (HIC) Animal Model (continued).

Type	Product	Model	Outcomes and findings			Reference
			Measurement	Mechanism	Efficacy	
TCM	Morus alba L.	Male Swiss albino mice	Catalepsy↑	N.D.	Haloperidol (1 mg/kg, i.p.) was administrated to mice (n = 6) pre-treated with vehicle or Morus alba extract (MAE) (50, 100 and 200 mg/kg, i.p.). The duration of catalepsy was measured at 0, 30, 60, 90, 120, 150, and 180 min using the bar test. The results showed that the MAE significantly potentiated HIC at each time interval in dose dependent manner. MAE at dose 50, 100 and 200 mg/kg showed maximum cataleptic score 275.8 ± 9.998, 290.3 ± 5.852 and 291.2 ± 5.288 s respectively at 120 min in haloperidol treated animals.	(Yadav and Nade, 2008)
TCM	Cassia sophera Linn	Swiss albino mice	Catalepsy ∆	N.D.	The effect of Cassia sophera fractions on HIC was studied using bar test. Mice in test groups (n = 6) received the ethanol extract, fractions with chloroform, ehyl acetate and ethanol (750 mg/kg, p.o.). Haloperidol (1 mg/kg, s.c.) was used to induce catalepsy and the duration of catalepsy were measured at 15, 30, 60, 90, 120, 150 and 180 min. No significant decrease in the duration of catalepsy was showed in the result.	(Nagore et al., 2009)
TCM	Acorus calamus Linn	Swiss albino mice	Catalepsy↑	N.D.	The effect of methanol (ACME) and acetone (ACAE) extract of Acorus calamus leaves against HIC have been studied in mice (n = 6). All four groups received haloperidol administration with a dose of 0.1 mg/kg (i.p.), ACME and ACAE at the dose of 5, 20, 50 mg/kg (p.o.) respectively were administered to all groups except the control group. The results showed that ACME at the dose of 50 mg/kg and ACAE at the dose of 20 and 50 mg/kg significantly potentiated the haloperidol induced catalepsy.	(Ka et al., 2009)
TCM	Ageratum conyzoides Linn	Swiss albino mice	Catalepsy ∆	N.D.	The effect of Ageratum conyzoides on HIC in mice (n = 6) has been studied using the bar test. Animals in 3 different groups received hydroalcoholic extract of Ageratum conyzoides in doses 250, 500 and 1000 mg/kg (p.o.) respectively while the other groups received vehicle or standard drug. One hour after the drug administration, all the groups received haloperidol (1 mg/kg, i.p.) and the duration of catalepsy was measured at 15, 30, 60, 90, 120, 150 and 180 min. No significant inhibition of the HIC was observed in the test.	(Tote et al., 2009)
TCM	Piper betle	Male Swiss albino mice	Catalepsy↑	Dopamine transmission might be inhibited by the hydroalcoholic extract of Piper betel.	Hydroalcoholic extract of Piper betel (PB) (100, 200 and 400 mg/kg) were administered to mice 60 min before haloperidol (1 mg/kg, i.p.). Forepaws of the animals were then placed on an elevated rod. Duration for which the mice retains the forepaws on the elevated rod was noted down. PB (400 mg/kg) treatment showed significant potentiation of epilepsy from 30 to 120 min. The lower two doses of PB (100 and 200 mg/kg) did not show any significant potentiation.	(Vyawahare and Bodhankar, 2007)

Table 2. Effect of HNPs on Haloperidol-induced Catalepsy (HIC) Animal Model (continued).

Type	Product	Model	Outcomes and findings			Reference
			Measurement	Mechanism	Efficacy	
TCM	Ginkgo biloba L.	Swiss albino mice	Catalepsy↑	N.D.	The effect of Ginkgo biloba Extract EGb 761 on catalepsy induced by haloperidol was studied in mice (n = 8–12). In the acute study, 40, 80 or 160 mg/kg EGb 761 (p.o.) were administered followed by 2 mg/kg haloperidol (i.p.) 30 min later. Repeated treatment with EGb 761 was performed for 5 days in the chronic study. Haloperidol was administered on day 1 and day 5. Acute treatment of EGb 761 with HIC throughout the experiment except for the EGb dose of 80 mg/kg at 10 min. EGb 761 with the dosage of 40 mg/kg enhanced the cataleptic effect of haloperidol at 10 min compared with the control group. Repeated administration of EGb 761 (80 mg/kg) potentiated HIC at 10 min. The results showed that repeated treatment with EGb 761 enhanced catalepsy caused by haloperidol.	(Fontana et al., 2005)
TCM	Hibiscus rosa-sinensis	Swiss albino mice	Catalepsy↑	HRS may be involved in decreasing dopaminergic transmission	Bar test was used to study the interaction between Hibiscus rosa-sinensis (HRS) and haloperidol. HRS (50, 100 and 200 mg/kg, i.p.) was administered to the animals 30 min prior to administration of haloperidol (1 mg/kg, i.p.). The duration of catalepsy was measured at 0, 30, 60, 90, 120, 150 and 180 min. The results showed that HRS significantly potentiated HIC at each time interval.	(Nade et al., 2009)
HP	BR-16A (A herbal psychotropic preparation) [2]	Laca mice	Catalepsy↓	The anticataleptic effect of BR-16A may be due to Withania somnifera present in the formulation.	The effect of BR-16A (50 and 100 mg/kg, p.o.) Against haloperidol (1 mg/kg, i.p.) induced catalepsy was studied on mice. Catalepsy score was measured for 4 h at one-hour intervals after haloperidol. BR-16A significantly reduced severity of HIC at all time intervals. Aahwagandha (50 and 100 mg/kg, p.o.), the major constituent of BR-16A, significantly and dose dependently reduced cataleptic score as compared to haloperidol alone treated animals at 60, 120 and 180 min.	(Kumar and Kulkarni, 2006)
HP	Pueraria tuberosa	Albino rats	Catalepsy ∆	ALE and AQE elicited significant nootropic effect by interacting with cholinergic, GABAnergic, adrenergic and serotonergic systems. The extracts neither facilitated nor blocked release of the dopamine.	Rats (n = 6) received distilled water (10 ml/kg, p.o.) as control, haloperidol (1mg/kg, i.p.), alcoholic extract of P. Tuberosa (ALE) (50, 75, 100 mg/kg, p.o.) and aqueous extract of P. Tuberosa (AQE) (100, 200, 400 mg/kg, p.o.) respectively. Bar test was used to evaluate cataleptic activity at 0, 30, 60, 90, 120, 150 and 180 min. All the doses of ALE and AQE neither reduced nor potentiated HIC at all time intervals.	(Rao et al., 2008)
HP	Smilax zeylanica L.	Wistar rats	Generation of thiobarbituric acid reactive substances↓, glutathione↑, catalepsy↓, SOD levels↑	Treatment with SZ significantly increased the activity of enzymes by quenching the free radicals and restored the peroxides and antioxidant levels to near normal in the brains of the test animals.	Smilax zeylanica L. (SZ) (dose of 100, 250, 500 mg/kg) was administrated for 15 days in rats. Catalepsy was induced by haloperidol (1 mg/kg, i.p.). The result showed that HIC was significantly reversed by co-administration of SZ. The maximal decrease in catalepsy was observed in the SZ group at a dose of 500 mg/kg.	(Rasheed et al., 2012)
		Wistar rats	Catalepsy↓	N.D.	Haloperidol (1 mg/kg) was administered to induce catalepsy in rats. The extract of SZ significantly reversed HIC in bar test. The maximal decrease was observed in the group receiving alcoholic extract of SZ at a dose of 500 mg/kg. Oral administration of the extract along with haloperidol significantly restored the peroxides and antioxidant levels to near normal in the brain of the test animals.	(Shaik et al., 2012)

Table 2. Effect of HNPs on Haloperidol-induced Catalepsy (HIC) Animal Model (continued).

Type	Product	Model	Outcomes and findings			Reference
			Measurement	Mechanism	Efficacy	
HP	Bauhinia tomentosa L.	Swiss albino mice	Catalepsy↓	Ethanol extract of Bauhinia tomentosa (EEBT) possessed anti-anxiety and depressant activity in mice	Haloperidol (2 mg/kg, i.p.) was administered to mice 30 min after ethanol extract of EEBT (200 and 400 mg/kg, p.o.) treatment in the bar test. The result showed that EEBT in a dose of 200 mg/kg potentiates the HIC initially after 30 min of haloperidol treatment. However, the catalepsy score was significantly decreased after 90 min of haloperidol administration. EEBT in a dose of 400 mg/kg did not show any significant potentiation of catalepsy after 30 min but decreased the score significantly after 90 min.	(Sathya et al., 2011)
HP	Hemidesmus indicus	Rats	Catalepsy↑	N.D.	The aqueous extract of roots of Hemidesmusindicus (AERHI) was administered orally at a dose of 100, 300 and 500 mg/kg for a period of 30 days. Haloperidol induced catalepsy models were used. AERHI significantly potentiated the HIC	(Madhu et al., 2017)
HP	Desmodium adscendens	Mice	Catalepsy↑	N.D.	Desmodium adscendens extract (DAE) did not induce any cataleptic event in naïve mice but only significantly enhanced HIC at a dose of 1000 mg/kg.	(Amoateng et al., 2017a)
HP	Synedrella nodiflora	Female ICR mice	Catalepsy↑ Locomotion↓	N.D.	The central nervous system activities of Synedrella nodiflora extract (SNE) (30–3000 mg/kg, p.o.) were investigated. SNE potentiated the effects of haloperidol and chlorpromazine on apomorphine-induced cage climbing and stereotypy activities in mice.	(Amoateng et al., 2017b)
HP	Trichilia catigua	Male Swiss mice	Catalepsy↓	T. Catigua (TC) extract has stimulating effects upon the dopaminergic system. It inhibits dopamine uptake and increase dopamine release.	The bar test was used to evaluate the effects of TC extract on the catalepsy induced by haloperidol. Mice were pre-treated with TC extract (200 mg/kg, p.o.) or PBS (10 ml/kg, p.o.) followed by haloperidol administration (4 mg/kg, i.p.). The result showed that catalepsy induced by haloperidol was significantly decreased by pre-treatment with TC extract.	(Viana et al., 2011)
HP	Phyllanthus maderaspatens is L.	Male albino mice	Catalepsy ∆	Phyllanthus maderaspatensis (PM) does not have activity on dopaminergic transmission.	Bar test was used to study the interaction between aqueous extract of PM and haloperidol. Haloperidol (1 mg/kg, i.p.) was injected to mice pre-treated 30 min before with vehicle or aqueous extract of PM (50 mg/kg, i.p.). The result showed no significant affect between PM and vehicle.	(Nirmal et al., 2009)
HP	Mucuna pruriens	Male mice	Catalepsy↓	N.D.	The M. pruriens seed extract at doses of 200 mg/kg was orally administrated. The catalepsy observation was performed 60 min after the administration of haloperidol. The intensity of the catalepsy was measured as the time of the mice hang on a 15 cm height rod. Catalepsy test showed that extract was able to lower the catalepsy in mice.	(Sardjono et al., 2018)
		Adult albino rats	Catalepsy↓	The anticataleptic effect of Mucuna pruriens (MP) may be due to MP contain dopamine and 5-HT.	Haloperidol (1 mg/kg, i.p.) was used to induce catalepsy. MP at a dose of 50, 100 and 200 mg/kg was administered orally to three respective group 1 h prior to haloperidol administration. The result showed a significant reduction in the cataleptic score of the studied animals.	(Champatisingh et al., 2011)

Table 2. Effect of HNPs on Haloperidol-induced Catalepsy (HIC) Animal Model (continued).

Type	Product	Model	Outcomes and findings			Reference
			Measurement	Mechanism	Efficacy	
HP	Withania somnifera	Male Swiss albino mice	Catalepsy↓	The antioxidant properties of Withania somnifera (WS) may be responsible for the anticataleptic effect of WS. The reduction in SOD activity in brain may be due to the antioxidant phytochemical constituents of WS	The acute and chronic anticataleptic effect of WS extract on HIC in mice (n = 6) was evaluated. The acute treatment group received WS extract (1.7, 4.25, 8.5 mg/kg) 30 min prior to haloperidol and standard bar test was used to measure catalepsy. The chronic treatment group received the drugs for 6 days. Result showed that WS reduced cataleptic score in a dose dependent manner, both in the acute and chronic study. SOD activity was also lowered in the WS (4.25, 85 mg/kg) group.	(Nair et al., 2008)
		Male Swiss albino mice	Catalepsy↓	N.D.	Vehicle or WS (20-200 mg/kg, p.o., n = 6) was administrated to the mice 60 min before haloperidol (1 mg/kg, i.p.). Mice were subjected to the bar test 30 min later. WS (20 or 50 mg/kg) showed insignificant protection against HIC while WS (100 or 200 mg/kg) significantly and dose dependently decreased cataleptic score on the bar test as compared to control group.	(Girdhari and Avtar, 2009)
HP	Anacyclus pyrethrum	Male Swiss albino mice	Catalepsy↓	AP root extract might produce antidepressant effect either by interaction with adrenergic or dopamine receptor.	Haloperidol (1 mg/kg) was administered to mice 30 min after the Anacyclus pyrethrum (AP) root extract (50, 100, 200 mg/kg, p.o.). The result showed AP extract significantly reduced the duration of catalepsy induced by haloperidol.	(Badhe et al., 2010)
HP	Emblica officinalis	Albino mice	Catalepsy↓	The anticataleptic effects of Emblica officinalis (EO) might be due to both its anticholinergic and antioxidant properties. It quenches free radicals and reduce the oxidative stress induced by haloperidol in the brain tissue	The protective effect of the aqueous extract of EO on HIC in mice (n = 6) was examined. The effects of EO (0.8, 2.0 and 4.0 mg/kg) and the standard drugs scopolamine (1.0 mg/kg) and ondansetron (0.5, 1.0 mg/kg) were assessed after 7 days, 30 mins prior to the haloperidol. A standard bar test was used to evaluate cataleptic activities at 30 min intervals until 120 min and at the end of experiment at 240 min. Result showed that there is a significant reduction in the cataleptic scores and oxidative stress in all test drug treated group versus control. EO was more protective against HIC at doses 2.0 and 4.0 mg/kg versus standard drugs. Maximum reduction in SOD activity was seen at EO 4.0 mg/kg.	(Sudhakar et al., 2009)
HP	Randia dumetorum	Male albino mice	Catalepsy Δ	The ethanolic extract of Randia dumetorum (RD) fruit does not possess antidopaminergic and anti-serotonergic activity and so does not inhibit haloperidol induced catalepsy.	The anticataleptic efficacy of ethanolic extract of RD fruits in HIC in mice (n = 5) was evaluated. Different experimental groups were administered haloperidol (1 mg/kg, i.p.) 1 h after the treatment with gum acacia (1%, p.o.) as vehicle control, chlorpheniramine maleate (10 mg/kg, i.p.) and ethanolic extract of RD (180, 360 and 720 mg/kg, p.o.) respectively. Bar test was used to evaluate HIC at 15, 30, 60, 90, 120, 150 and 180 min. Result showed that RD did not inhibit HIC in mice.	(Ghaisas et al., 2008)
HP	Ficus bengalensis Bark	Male albino mice	Catalepsy Δ	The extract may not have activity on dopaminergic transmission.	The effect of various extracts of Ficus bengalensis Bark on haloperidol-induced cataleptic activity was evaluated using a bar test. Haloperidol (1 mg/kg, i.p.) was injected to mice (n = 5) before administration of vehicles or Ficus bengalensis Bark (5 mg/kg. i.p.). The duration of catalepsy was measured. Result showed that none of the extracts inhibit HIC.	(Taur et al., 2007)

Table 2. Effect of HNPs on Haloperidol-induced Catalepsy (HIC) Animal Model (continued).

Type	Product	Model	Outcomes and findings			Reference
			Measurement	Mechanism	Efficacy	
HP	Nelumbo nucifera	Rats	Catalepsy↓	Hanging antioxidant enzymes level such as SOD, glutathione peroxidase and catalase by quenching the free radicals to combat oxidative stress in brain tissue.	Catalepsy was induced by administration of haloperidol (1 mg/kg, i.p.) in male albino rats. A significant reduction in the cataleptic scores were observed in all the drug-treated groups as compared to the haloperidol alone treated group; with maximum reduction observed in the Nelumbo nucifera (200 and 400 mg/kg body weight) administered group.	(Reddy and Singhal, 2014)
HP	Beta vulgaris L.	Rats	Catalepsy↓	The ability of the drug to potentiate dopaminergic transmission in the striatum.	Pre-treatment with methanol extract of Beta vulgaris 200 and 300 mg/kg significantly reduced the duration of catalepsy induced by haloperidol as compared to haloperidol alone treated group.	(Nade et al., 2015)
HP	Murraya koenigii	Male albino mice	Catalepsy↓, SOD, catalase↑	The antioxidant activity of MEMK may be due to the presence of flavonoids and phenolic compounds. MEMK reversed the changes in the antioxidant enzyme levels (SOD, catalase).	The effect of methanol extraction of Murraya koenigii (MEMK) on the HIC was studied in mice and a phytochemical screening of MEMK was performed. They received MEMK (30, 100, 200 mg/kg, p.o.) at 1 h before receiving haloperidol (1 mg/kg, i.p.). Bar test was used to measure cataleptic activity for 3 h. Result showed a significantly reduction in HIC and reversed the reduction in the forebrain GSH levels in the MEMK-treated group.	(Patil et al., 2012)
HP	Plumbago zeylanica L, and Camellia sinensis	Rats	Catalepsy↓	Phytoconstituents like natural L-dopa, alkaloids and polyphenols have been reported in this plant which might be responsible for the above behavioural effects.	Haloperidol induced a time dependent increase in cataleptic score in rats, as compared to vehicle treated groups. All the groups including L-dopa and carbidopa (Syndopa), hydro-alcoholic extract of P. zeylanica alone and its combination with C. sinensis showed significantly lower scores of catalepsy at all time periods as compared to haloperidol alone.	(Ittiyavirah and Ruby, 2014)
HP	Momordica dioica	Male albino mice	Catalepsy ∆	N.D.	Haloperidol (1 mg/kg, i.p.) was injected to mice pre-treated 30 min before with vehicle, petroleum ether, ethyl acetate, methanol and aqueous extracts of Momordica dioica seed (50 mg/kg, i.p., each). None of all extracts inhibited HIC.	(Maharudra et al., 2011)
HP	Canscora decussate	Mice	Catalepsy↓	Hanging antioxidant enzymes (SOD, glutathione peroxidase and catalase) level and quenching the free radicals to combat oxidative stress in brain tissue.	All these assessments were done on 24 mice which were divided into 4 groups (n = 6). Methanol extract of Canscora Decussate (CD) was administered at 100 mg/kg and 200 mg/kg, 30 min prior to haloperidol treatment for 7 days. CD significantly improved the behavioural activities and striatal antioxidant status in a dose dependent manner.	(Tamilanban et al., 2015)
F	Caffeine	Mae Wistar rats	Catalepsy↓	N.D.	The effect of chronic caffeine treatment on HIC was measured. Rats were treated with caffeine or water for 6 months. They were evaluated in the catalepsy bar test from day 18–27 after caffeine withdrawal. Haloperidol (1mg/kg, s.c.) was injected to induce catalepsy. Result showed that the average cataleptic immobility was lower in the caffeine-treated rats and they also had higher catalepsy latency scores compared with control rats.	(Narita et al., 1982)

Table 2. Effect of HNPs on Haloperidol-induced Catalepsy (HIC) Animal Model (continued).

Type	Product	Model	Outcomes and findings			Reference
			Measurement	Mechanism	Efficacy	
F	Alpha lipoic acid	Male albino Wistar rats	TD, catalepsy↓ locomotor activity↑, lipid oxidation↓	ALA and its metabolite dihydro lipoic acid have antioxidative properties which scavenge reaction oxygen species and reactive nitrogen species.	The effect of Alpha lipoic acid (ALA) on haloperidol induced TD, their impact on oxidative stress and lipid peroxidation was examined. Haloperidol (1mg/kg/i.p.) was administered to rats for 21 days to induce VCM and catalepsy. ALA at doses of 25, 50, 100 mg/kg p.o. were tested. Result showed that supplementation with ALA decrease haloperidol-induced TD (100 mg/kg) and catalepsy (dose-dependent) significantly. ALA reversed the haloperidol-induced decrease in locomotor activity at all doses and reverse the haloperidol-induced lipid oxidation (100 mg/kg).	(Thaakur and Hummabindhu, 2009)
F	Vitamin E and Vitamin C	Male Swiss mice	Catalepsy↑	Vitamin E inhibits inducible protein kinase C activity in smooth muscle cells and completely preventing glutamate-induced cell death without decreasing glutamate-induced accumulation of intracellular peroxides.	The effect of vitamin C and E on HIC was evaluated in mice using the hanging-bar test. Mice were pre-treated with vitamin E (3–100 mg/kg, i.p.) or vehicle, followed by haloperidol (1 mg/kg, i.p.) 30 min later. The result shows that vitamin C pre-treatment potentiated the catalepsy induced by haloperidol in a dose-dependent manner. The result shows that vitamin E potentiated the catalepsy produced by haloperidol only at the dose of 100 mg/kg.	(Lazzarini et al., 2005)
F	Carya illinoensis	Male Wistar rats	Catalepsy↓, OD↓	N.D.	Aqueous extract of pecan nut shell (AE) or water were administered to rats ad libitum. After 4 weeks of oral treatment, the rats received either vehicle or haloperidol (12 mg/kg/ml, i.m.) once a week for 28 days, totalizing four doses. The result showed that AE was able to prevent OD development compared to the control. The effect of AE on the reversal of OD and HIC was also tested. The AE treatment was able to reverse the OD and HIC.	(Trevizol et al., 2011)
F	Ascorbic acid	Female Sprague Dawley rats	Catalepsy↑	Ascorbic acid might have blocking effect on dopaminergic transmission	Rats were given ascorbic acid (1000 mg/kg, i.p.) followed in 15 min by haloperidol (0.2 mg/kg, s.c.), compared with control (acidified saline). Catalepsy was measured every 30 mins for up to 120 min. Result found that the combined use in progressively more cataleptic activities.	(Dorris and Dill, 1986)
		Adult male squirrel monkeys	Catalepsy↑	Ascorbic acid might have blocking effect on dopaminergic transmission	Monkeys were given ascorbic acid (100 mg/kg, i.p.) followed in 1 h by haloperidol (0.1 mg/kg, s.c.). Result found that there was increased catalepsy induced by haloperidol when combined in ascorbic acid.	

Notes: [1] Contains: Hebulae Fructus, Terminaliae belliricae Fructus, Phyllathus emblica Officinalis; [2] Contains: Bacopa monnieri, Centella asiatica, Acorus calamus, Withania somnifera, Tinospora cordifolia, Embelica officinalis, Evolvulus aisinoides, Saussurea lappa, Terminalia belerica, Terminalia chebula, Terminalia arjuna.
Abbreviation: N.D: not detected; TCM: traditional Chinses medicine; F: food and dietary supplements; HP: other herbal products; i.p.: intraperitoneal injection; p.o.: oral administration; i.v.: intravenous administration; s.c.: subcutaneous injection; i.m.: intramuscular injection TD: tardive dyskinesia; OD: orofacial dyskinesia; VCM: vacuous chewing movements; HIC: haloperidol-induced catalepsy; SOD: superoxide dismutase; 5-HT: 5-hydroxytryptamine.

Table 3. Preclinical Studies on Extrapyramidal Syndrome (EPS) Related Haloperidol-HNPs Interactions.

Type	Product	Measurement	Outcomes and findings		Reference
			Mechanism	Effect	
TCM	Nardostachys jatamansi	Parkinsonism↓	NJ enhance the bioavailability of circulating dopamine by up regulation of dopaminergic signalling.	The result showed no significantly organ damage caused by Nardostachys jatamansi (NJ) in haloperidol (1 mg/kg, i.p.) induced parkinsonism. The hydroalcoholic extract of NJ at a dose of 500 mg/kg has more significant effect than 250 mg/kg in the reversal of haloperidol induced parkinsonism.	(Rasheed et al., 2009)
TCM	Hippophae rhamnoides L.	Locomotor activity↑, food intake↓	N.D.	The result showed that Hippophae rhamnoides L. (HRL) significantly lower food intake in rats treated with repeated haloperidol. Significant increases were observed in rats repeatedly treated with haloperidol plus orally supplemented with HRL. Plasma tryptophan showed no significant interaction between the drugs while brain tryptophan showed significant interaction between HRL and drug. 5-HT levels were also significantly increased by HRL in haloperidol injected rats.	(Batool et al., 2009)
TCM	Valeriana officinalis	VCM ∆, locomotor activity ∆	Co-treatment of VO and haloperidol did not alter the oxidative stress parameters nor protect against haloperidol-induced dopamine uptake reduction in rats.	The result showed that Valeriana officinalis (VO) was not able to reduce neither the prevalence nor the intensity of VCM. The co-administration of VO and haloperidol also failed to prevent or alter the decrease on locomotor activity. VO did not cause any significant changes in the plus maze test compared to haloperidol alone treated group.	(Fachinetto et al., 2007)
TCM	Morus alba L.	VCM↓, TD↓, catalase↑, lipid peroxidation↑	MAE may have free radical scavenging activity, thereby decreasing the lipid peroxidation levels and sparing the antioxidant enzymes SOD and catalase.	The results showed that chronic concomitant administration of Morus alba extract (MAE) significantly attenuated the haloperidol induced VCM and tongue protrusions dose-dependently. The co-administration significantly increased catalase and attenuated lipid peroxidation compared with rats treated with haloperidol only.	(Nade et al., 2010)
HP	Ilex paraguariensis	VCM↓, OD↓, memory dysfunction↓	The antioxidant properties of IP may be responsible for the reduction in OD induced by haloperidol.	Result showed that co-administration of Ilex paraguariensis (IP) extract and haloperidol reduced the frequency of VCM and showed a significant improvement in the process of spatial learning.	(Colpo et al., 2007)
HP	Khat (leaves and buds of Catha edulis Forsk)	Head twitches∆, spontaneous motor activities↑	N.D.	Result showed that haloperidol did not affect the head twitch response to Khat or amphetamine but enhanced spontaneous motor activity.	(Connor et al., 2002)

Table 3. Preclinical Studies on Extrapyramidal Syndrome (EPS) Related Haloperidol-HNPs Interactions (continued).

Type	Product	Measurement	Outcomes and findings		Reference
			Mechanism	Effect	
HP	Withania somnifera	Involuntary orofacial movements↓ TD↓	The protective effect of WSG from neuroleptic-induced TD is possibly due to its antioxidant effect rather than its GABA-mimetic action	Result showed that Glycowithanolides from Withania somnifera (WSG) (100 and 200 mg, p.o.), administered concomitantly with haloperidol for 28 days inhibited the induction of the neuroleptic TD.	(Bhattacharya et al., 2002)
		VCM↓, OD↓, lipid peroxidation↓, super oxide dismutase↑, catalase↑	WS root extract may possess antioxidant action and have free radical scavenging activity.	Result showed that chronic co-administration of Withania Somnifera (WS) root extract with haloperidol does-dependently suppressed the haloperidol-induced VCMs and tongue protrusions, reversed the extent of lipid peroxidation and significantly reversed the haloperidol-induced decrease in forebrain SOD and catalase. There was no significant effect on haloperidol-induced decrease in glutathione level.	(Naidu et al., 2003)
HP	Ashwagandha, Tulsi and Haldi [1]	TD↓	The herbal formulation influence dopamine receptor-mediated neurotransmission and serotonergic receptor-mediated neurotransmission.	The formulation demonstrated protective effect against haloperidol induced catalepsy and bradykinesia. No mortality, no adverse changes in behaviour of animals as well as no abnormalities were detected in experimental mice	(Pingale and Prabhavalkar, 2015)
F	Natto (Fermented Soybean)	Locomotor activity↓	The dopaminergic pathway probably involves in the enhancement effect in locomotor activity induced by Natto.	Haloperidol (1 mg/kg, i.p.) was administered 15 min before locomotor activity measurement. Result showed that haloperidol attenuated the Natto-induced hyperlocotion in mice.	(Mamiya and Nishimura, 2007)
F	Brassica oleracea	lipid peroxidation↓, TD↓	The result suggested the role of free radicals in the pathophysiology of the haloperidol-induced EPS.	Hydroalcoholic extract of B. oleracea (250 and 500 mg/kg, p.o.) decreased the elevated levels of lipid peroxidation in the haloperidol-treated animals and elevated the cellular defence mechanisms such as glutathione.	(Nagarjuna et al., 2015)
F	Murraya koenigii	Locomotor activity↑, SOD↑, catalase, glutathione↑	The treatment of EEMK and AMK reversed the haloperidol-induced decrease in forebrain SOD and catalase levels.	The result showed that treatment with ethanol extract of Murraya koenigii (EEMK) and aqueous of Murraya koenigii (AMK) significantly increased the number of squares traversed and reduced the number of grooming. Co-administration of EEMK also significantly restored the haloperidol-induced body weight lost.	(Patil et al., 2012)

Table 3. Preclinical Studies on Extrapyramidal Syndrome (EPS) Related Haloperidol-HNPs Interactions (continued).

Type	Product	Measurement	Outcomes and findings		Reference
			Mechanism	Effect	
F	Spirulina	Oxidative stress↓, SOD↓, TD↓, VCM↓	Spirulina is a cocktail of potent antioxidants, the enzymatic and non-enzymatic oxidants it contains may act synergistically to protect against haloperidol induced oxidative stress and thereby decreasing oxidative stress induced TD.	Spirulina (45, 90, 180 mg/kg) significantly decreased dyskinetic movements developed by haloperidol and maintained it till 49th day when compared to the haloperidol alone group. Spirulina at a dose of 180 mg/kg did not completely reverse the haloperidol induced dyskinetic movements. The decreased SOD caused by chronic haloperidol were significantly reversed by 180 mg/kg of Spirulina. Spirulina (90 and 180 mg/kg) significantly reversed the decreased catalase levels. The total antioxidant status decreased by chronic haloperidol was significantly increased by Spirulina at all three doses. The haloperidol increased lipid peroxidation was not reversed by 45 and 90 mg/kg of Spirulina whereas significantly decreased by 180 mg/kg of Spirulina. In conclusion, Spirulina treatment at the dose of 45, 90 and 180 mg/kg significantly reversed the chronic haloperidol increased frequencies of VCM in rats.	(Thaakur and Jyothi, 2007)
F	Carya illinoensis	Catalepsy↓, OD↓	N.D.	The result showed that aqueous extract of pecan nut shell (AE) was able to prevent OD development compared to the control. Haloperidol (12 mg/kg/ml, i.m.) or vehicle were administered to the rats once a week for 4 weeks. The rats later received AE or water, ad libitum, for 14 days. The AE treatment was able to reverse the OD and catalepsy induced by haloperidol.	(Trevizol et al., 2011)
F	Eclipta alba	EPS movement disorders↓	Eclipta alba elevated the cellular defence mechanism such as glutathione that proves its anticataleptic activity.	The antioxidant properties of Eclipta alba reduced the duration of catalepsy, number of VCM, decreased the elevated levels of lipid peroxidation in the haloperidol treatment groups.	(Jena et al., 2013)
F	Alpha lipoic acid	TD↓, catalepsy↓, locomotor activity↑, lipid oxidation↓	ALA and its metabolite dihydro lipoic acid scavenge reaction oxygen species and reactive nitrogen species.	Result showed that supplementation with ALA decrease haloperidol-induced TD (100 mg/kg) and catalepsy significantly. Alpha lipoic acid (ALA) reversed the haloperidol-induced decrease in locomotor activity at all doses and reverse the haloperidol-induced lipid oxidation (100 mg/kg).	(Thaakur and Hummabindhu, 2009)

Note: [1] Contains: roots of Withania somnifera, leaves of Ocimum sanctum, and rhizome of Curcuma longa.
Abbreviation: N.D: not detected; TCM: traditional Chinses medicine; F: food and dietary supplements; HP: other herbal products; i.p.: intraperitoneal injection; p.o.: oral administration; i.v.: intravenous administration; s.c.: subcutaneous injection; i.m.: intramuscular injection TD: tardive dyskinesia; OD: orofacial dyskinesia; VCM: vacuous chewing movements; SOD: superoxide dismutase.

bioavailability of circulating dopamine (Rasheed et al., 2009). Hippophae rhamnoides L., Alpha lipoic acid and Murraya koenigii showed reversal effect on haloperidol-induced increase locomotor activity (Batool et al., 2009; Patil et al., 2012; Thaakur and Hummabindhu, 2009). Hippophae rhamnoides L. also showed lower food intake when co-administered with haloperidol and significantly reversed haloperidol-induced decrease in brain tryptophan and 5-HT by normalizing the level of serotonergic influence on the activity of dopaminergic neurons (Batool et al., 2009). Murraya koenigii also showed similar reversal effect on locomotion as well as the haloperidol-induced decrease in forebrain SOD (superoxide dismutase) and catalase levels, reduced the lactoperoxidase and restored the decreased glutathione level (Patil et al., 2012). Free radical scavenging was suggested as one of the possible contributing factors to such effect, and it is also responsible for the alpha lipoic acid reversal of haloperidol-induced increase in locomotor activity (Thaakur and Hummabindhu, 2009). Fermented Soybean (Natto), a traditional Japanese food was used to induce hyperlocomotion in mice; however, haloperidol administration attenuated such effect with mechanism remains unknown (Mamiya and Nishimura, 2007). The fresh leaves and buds of Catha edulis Forsk, as known as Khat, are able to induce spontaneous motor activity and head twitch responses in mice, and pre-treatment of haloperidol had no effect on the head twitch response but enhanced spontaneous motor activity by unknown mechanism (Connor et al., 2002). As TD is one of the most commonly seen EPS that can be induced by haloperidol, HNPs that contain antioxidant properties and essential fatty acids are reported to decrease the incidence of TD and oxidative stress induced by haloperidol (Mahadik and Gowda, 1996; Mahadik and Scheffer, 1996; Mahadik et al., 2001; Reddy and Yao, 1996). In the present review, spirulina maxima, pecan nut shell (Carya illinoensis), Ilex paraguariensis, Withania somnifera and Morus alba showed antioxidant potential and significantly reversed the haloperidol-induced TD (Bhattacharya et al., 2002; Colpo et al., 2007; Nade et al., 2010; Naidu et al., 2003; Trevizol et al., 2011). On the other hand, although Valeriana officinalis demonstrated anxiolytic-like effect by reversing the haloperidol-induced increase in locomotor activity on rats, it failed to show significant effect on TD (Fachinetto et al., 2007).

A total of nine clinical studies were included in the current review with schizophrenic or EPS related symptoms as outcome measure (Table 4). Out of these trials, ascorbic acid, grape fruit juice and Vitamin E showed no significant effect on schizophrenic symptoms or EPS symptoms. In a double-blind, placebo-controlled study, male chronic schizophrenia subjects receiving haloperidol (0.4 mg/kg/day) in presence and absence of ascorbic acid (4.5 g/day) showed no significant difference in psychopathology (measuring by the PSAS score) or pharmacokinetics of haloperidol (Straw et al., 1989). In a randomized open-labelled controlled trial on twenty-four male psychosis patients receiving haloperidol 10 mg/day with or without vitamin E (3200 IU/day), vitamin E co-administration showed neither protective effect towards the haloperidol-induced EPS nor interference with the therapeutic effect of haloperidol (Eranti et al., 1998). In an open-label pilot study involved twelve female schizophrenia patients administered long-term haloperidol (6 mg bid for 3–31 weeks), and co-administered with grape fruit juice (200 ml, tid, for 7 days), the plasma concentration of haloperidol and the metabolite reduced haloperidol showed no significant change after grape fruit juice treatment, and the concentration ratios of the two remained unchanged throughout the study. The author suggested that such result might be due to the limited effect of intestinal CYP3A4 on the first-pass metabolism of haloperidol (Yasui et al., 1999).

On the other hand, three double-blind randomized control trials by Zhang et al. with high quality and low risk of bias investigated the effect of Ginkgo biloba (GB) (360 mg/day) on schizophrenic patients received a stable dose of haloperidol (0.25 mg/kg per day). The results demonstrated that GB treatment enhance the antipsychotic effect of haloperidol compared with the control group, probably due to antioxidant or free radical scavenger effect of GB and improve immune function of schizophrenia patients via the increase of CD3+, CD4+, IL-2-secreting cells as well as the CD4/CD8 ratio (Zhang et al., 2001a; Zhang et al., 2001b; Zhang et al., 2006). Yi Gan San (TCM formulae that containing Bulpeuri Radix, Poria, Chuanxiong Rhizoma, Glycyrrhizae Radix et Rhizoma, Angelicae Sinensis Radix, Uncariae Ramulus cum Uncis and Atractylodis Rhizoma) was reported to significantly reduce the psychiatric symptoms of 34 patients in an open label study. Schizophrenic patients received a stable dose of antipsychotic medication (haloperidol included) with Yi Gan San powder (1.5 g of extract, 1–3 times per day) for 4 weeks demonstrated significant decrease of schizophrenia subscale score but not the drug-induced EPS scale score in the patients compared with the control group (Miyaoka et al., 2009). It was suggested that activities on serotonergic and glutaminergic systems might be the major contributor of the therapeutic effects of Yi Gan San. Another open-label pilot study with 17 paranoid schizophrenia patients received long-term haloperidol treatment with 1000 mg ω-3 fatty acids (eicosapentaenoic acid 180 mg + docosahexaenoic acid 120 mg, bid), vitamin E (400 IU, bid) and vitamin C (1000 mg/day) suggested that the co-administration significantly lowered the schizophrenic symptoms and EPS scores of the patients due to their anti-oxidative properties (Sivrioglu et al., 2007). In a non-interventional, observational, open-label trial using Kava special extract WS 1490 in psychiatric patients who received haloperidol treatment, the result showed significant improvement for EPS signs and symptoms with no mechanism mentioned (Boerner and Klement, 2004).

Table 4. Clinical Studies on Extrapyramidal Syndrome (EPS) Related Haloperidol-HNPs Interactions.

Type	Product	Studies design				Outcomes and findings		Country	Reference
		Subject	Design (sample size)	Jadad scale	Risk of bias	Measurement	Effect		
TCM	Ginkgo biloba L.	Schizophrenic patients	Double-blind randomized control (10)	4	Low	Peripheral immune function↑	Significant reduction in brief psychiatric rating scale (BPRS) was observed in both groups. The EGb group showed significant reduction in scale for assessment of positive symptoms (SAPS) and scale for assessment of negative symptoms (SANS) than the placebo group. There was a significant correlation between the change in CD4+ cells (before and after treatment) and the reduction of BPRS score in the whole patient group. The result suggests that EGb may improve the decreased peripheral immune functions in schizophrenia patients.	China	(Zhang et al., 2006)
		Schizophrenic patients	Double-blind randomized control (56)	4	Low	Anti-psychotic effect↑	The BPRS, SAPS, and SANS total score showed significant improvement in the EGb group between baseline and 12 weeks of treatment. Treatment emergent symptom scale (TESS) subscore 1 (behavioural toxicity) and subscore 3 (symptoms of nerve system) were significantly decreased in the EGb group compared with the placebo group. The results suggest that EGb treatment may be able to increase the effectiveness and reduce the side effects of haloperidol.	China	(Zhang et al., 2001a)
		Schizophrenic patients	Double-blind randomized control (43)	4	Low	Anti-psychotic effect↑	Significantly improved SAPS and SANS score was observed in EGb group while only sans scores were improved in the placebo group. The TESS total score in EGb group tended to be lower than that in placebo group ($p = 0.08$), the significant differences were observed in subscore 1 and subscore 3. The average SOD level decreased significantly in patients from EGb group after the treatment	China	(Zhang et al., 2001b)
TCM	Yi Gan San (YGS) [1]	Schizophrenic patients	Open-label study (34)	3	High	Psychiatric symptoms↓	The average daily YGS dosage was 6.7 ± 2.5 g with the highest proportion of patients being administered a daily dosage of 7.5 g. No adverse effects were caused by YGS treatment. The mean positive symptoms subscale score for treatment group on the positive and negative syndrome scale (PANSS) is 27.7 ± 6.1 while negative symptoms subscale score is 30.4 ± 5.8 and the general psycho-pathology subscale is 65.1 ± 5.4. The positive symptoms subscale score was reduced by 68.2% at 2 weeks and this reduction progressed by 43.0% at the 4th week. The PANSS negative symptoms subscale score was reduced by 73.7% at 2nd week and this reduction progressed by 59.9 at the 4th week. The PANSS general psycho-pathology subscale score was reduced by 70.5% at 2nd week and this reduction progressed by 60.8% at the 4th week. No change on the PANSS scales was observed in the control group. Mild and transient adverse events including nausea (2 cases) and tiredness (1 case) were reported by the subjects.	Japan	(Miyaoka et al., 2009)

Table 4. Clinical Studies on Extrapyramidal Syndrome (EPS) Related Haloperidol-HNPs Interactions (continued).

Type	Product	Studies design				Outcomes and findings		Country	Reference
		Subject	Design (sample size)	Jadad scale	Risk of bias	Measurement	Effect		
HP	Kava Special Extract (WS 1490)	Patients with psychiatric diagnoses	Non-interventional, observational, open-label study (42)	1	High	EPS signs and symptoms↓	Patients (17 female, 25 male) were pre-treated by neuroleptics. In both patient and physician questionnaires as well as in the physician's global ratings, significant improvements were found for all EPS symptoms recorded by WS 1490. The findings of this observational study suggest that EPS of neuroleptic drugs may be attenuated by Kava special extract WS 1490. Five adverse events reported.	Germany	(Boerner and Klement, 2004)
F	Vitamin E	Males patients with psychosis	Randomized controlled trial (24)	2	High	EPS symptoms Δ	The result showed that Vitamin E had no prophylactic effect on drug-induced EPS.	India	(Eranti et al., 1998)
F	Ascorbic Acid	Male chronic schizophrenia patients	Double-blind, placebo controlled (8)	3	Some concerns	PSAS score Δ	The result did not show any significant change in psychopathology in patients taking ascorbic acid and there was no significant pharmacokinetic interaction with haloperidol.	United State	(Straw et al., 1989)
F	Omega-3 Fatty Acids, Vitamin E, Vitamin C, Supplements	Paranoid schizophrenia patients, treated with haloperidol for at least 3 months	Open-label pilot study (17)	1	High	Schizophrenic symptoms↓, EPS side effects↓	Result showed a significant decrease in all the scale scores and SOD level was significantly lower at the end of study, suggesting that the supplementations have beneficial effects on positive and negative symptoms of schizophrenia and also reduce the haloperidol induced side effects.	Turkey	(Sivrioglu et al., 2007)
F	Grapefruit Juice	Schizophrenic patients	Open-label pilot study (12)	0	High	Schizophrenic symptoms Δ, side effect Δ	The BPRS scale and UKU side effect rating scales were used to assess clinical symptoms and side effects. Result showed that grapefruit juice did not alter the scores of BPRS scale and UKU side effect rating scale throughout the study.	Japan	(Yasui et al., 1999)

Note: [1] Contains: Bulpeuri Radix, Poria, Chuanxiong Rhizoma, Glycyrrhizae Radix et Rhizoma, Angelicae Sinensis Radix, Uncariae Ramulus cum Uncis, Atractylodis Rhizoma.
Abbreviation: N.D: not detected; TCM: traditional Chinses medicine; F: food and dietary supplements; HP: other herbal products; i.p.: intraperitoneal injection; p.o.: oral administration; i.v.: intravenous administration; s.c.: subcutaneous injection; i.m.: intramuscular injection TD: tardive dyskinesia; OD: orofacial dyskinesia; VCM: vacuous chewing movements; SOD: superoxide dismutase.

Table 5. Miscellaneous Haloperidol-HNPs Interactions on Animal Models.

Types	Product	Model	Outcomes and findings			Reference
			Measurement	Mechanism	Effect	
TCM	Solanum torvum	Male albino mice	Anxiolytic↓	ST might produce anxiolytic effect by interaction with α-adrenergic, serotonergic and dopamine receptors, increasing the level of norepinephrine, serotonin and dopamine in brain. Haloperidol antagonizes the dopamine D2-receptor and reverse the anxiolytic effect of ST.	The effect of a methanolic extract of S. torvum (ST) has been studied in combination with haloperidol in mice with elevated plus maze (EPM), light and dark transition apparatus (LDA), hole board apparatus (HBA) and marble burying test (MBT). The methanolic extract of ST (30, 100 mg/kg, i.p.) were given half an hour after administration of haloperidol (50 µg/kg, i.p.) for four consecutive days. The result showed that animals pre-treated with haloperidol produced significant increase in time spent and number of entries in open arm, decrease in time spent in closed arm in EPM test. In LDA test, haloperidol combined with ST produced a significant increase in time spent in light area and decrease in time spent in dark area. The combined drug produced significant increase in number of head poking in HBA and significantly decreased the number of burying response in MBT.	(Momin and Mohan, 2011)
TCM	Caihu-Sugan-San [1]	Male Sprague-Dawley rats	Immobility↑	Ferulic acid (FA) attenuated depression via selectively inhibiting dopamine reuptakes in brain	FA, the absorbed compound of Caihu-Sugan-San, was studied in combination with haloperidol. Pre-treatment with haloperidol (0.2 mg/kg, i.p.) was administered in rats 30 min before FA. The result showed FA-induced anti-immobility time was significantly reversed by the pre-treatment. This suggesting FA attenuated depression via inhibiting dopamine reuptakes in brain.	(Zhang et al., 2011c)
TCM	Calculus Bovis Sativus	Male Sprague Dawley rats	Anti-schizophrenia effects↑ locomotor activity↓, central distance↑	The enhanced oral bioavailability of haloperidol when combined with Calculus Bovis Sativus (CBS) might be attributed to the interaction between them.	An open field test was conducted to verify the pharmacodynamic effects of a combination treatment of CBS and haloperidol on MK-801-induced schizophrenic rats. Rat plasma concentrations of intragastric haloperidol and intravenous haloperidol were determined after oral administration of a single dose or 1-week of pretreatment with CBS (50 mg/kg). The pharmacodynamic data showed a significant decrease in locomotor activity and an increase in the percentage of the central distance when haloperidol was concomitantly administered with CBS compared with haloperidol administration alone.	(Lei et al., 2018)
TCM	Aegle marmelos	Albino mice	Immobility↑	Blockade of dopamine receptor by haloperidol increased duration of immobility and reversed antidepressant action of AM.	The effect of methanol extract of Aegle marmelos (AM) has been studied in combination with haloperidol in tail suspension test in mice (n = 6). Pre-treatment of haloperidol (0.1 mg/kg) caused significant increase in mean duration of immobility as compared to AM (150 mg/kg) alone. The result suggesting that haloperidol significantly attenuated the antidepressant effect of AM.	(Kothari et al., 2010)
HP	Hedyosmum brasiliense	Male Swiss mice	Immobility↑	The dopamine D1 and D2 receptors are involved in the anti-immobility action of haloperidol in the mouse forced swimming test.	Forced swimming test was used to investigate the influence of the dopaminergic system on the antidepressant-like effect of the Hedyosmum brasiliense (HB) extract. Haloperidol (0.2 mg/kg, i.p.) was administered 15 min before HB (50 mg/kg), and then tested in the forced swimming test 45 min later. The result showed that the anti-immobility effect of HB extract was significantly prevented by the pre-treatment of haloperidol.	(Gonçalves et al., 2012)

Table 5. Miscellaneous Haloperidol-HNPs Interactions on Animal Models (continued).

Types	Product	Model	Outcomes and findings			Reference
			Measurement	Mechanism	Effect	
HP	Ternstroemia pringlei Standl.	Adult male ICR mice	Sedation↑	N.D.	The mice was given aqueous extract of Ternstroemia pringlei and haloperidol (0.1–3 mg/kg) at different doses. The result shows that co-administration of Ternstroemia pringlei and haloperidol result in a synergistic sedative interaction.	(Balderas et al., 2008)
HP	Salvia sclarea	Sprague-Dawley rats	Anti-depressant↓	The anti-depressant-like effect of Salvia sclarea oil is likely mediated via a dopaminergic pathway.	The anti-depressant-like effects induced by 5% Salvia sclarea oil was significantly blocked by haloperidol (0.5 mg/kg).	(Seol et al., 2010)
HP	Asteracantha longifolia	Swiss albino rats	Iron deficiency anaemia↓	N.D.	Ethanolic extract of Asteracantha longifolia (AL) (100 and 200 mg/kg, i.p.) was administrated with haloperidol (0.2 mg/kg, i.p.) for 4 days to examine its effect on haloperidol induced iron deficiency anaemia. The result showed that haloperidol induced iron deficiency anaemia was reduced in a dose dependent manner by the treatment of AL. Compared with the control groups, the extract treated groups demonstrated significant increase in haematological parameters.	(Pawar et al., 2010)
HP	Vitex agnus Castus	Adult Balb/c male mice	Lutenizing hormone and testosterone level↓	VAC extract activates the dopaminergic pathway and inhibits hypothalamic–pituitary–gonadal axis and decreases luteinizing hormone and testosterone hormones.	Vitex agnus Castus (VAC) extract (365 mg/kg) and haloperidol (2 mg/kg) was i.p. injected alone respectively or together once daily for 30 days. Result showed that haloperidol alone increased luteinizing hormone and testosterone level vs. control and sham groups. Co-administration of VAC and haloperidol decreased luteinizing hormone and testosterone level. It was suggested that VAC extract can be used for pathological cases for increasing luteinizing hormone and testosterone.	(Nasri et al., 2007)
HP	Aridanin (isolated from Tetrapleura tetrapetra)	Swiss albino mice	hypothermic effect ∆	The hypothermic effect of aridanin is probably not mediated by the dopaminergic receptor system.	Mice were pre-treated with aridanin (15 and 30 mg/kg, p.o.) and haloperidol (0.1 mg/kg) was administered after. The result showed that haloperidol had no effect on the hypothermic activity of aridanin.	(Aderibigbe et al., 2007)
HP	Dracaena arborea	Male Wistar rats	Sexual stimulating effect↓	The sexual stimulating effect off Dracaena arborea (DA) may be mediated by the dopaminergic system.	The effects of DA on the sexual behaviour of gonado-intact and castrated sexually experienced rats are examined. Mice were pre-treated with haloperidol (10 mg/kg, i.p.) and were given a single oral dose of the ethanolic DA extract (100 mg/kg) to induce prosexual effect. Result showed that co-administration of haloperidol with the DA extract completely blocked the sexual behaviour (erection, intromission, ejaculation) of the rats induced by DA.	(Warcho et al., 2007)
HP	Aspidosperma ulei roots	Male Swiss mice	Pro-erectile effect↓	F3-5 induced penile erection probably involve the dopaminergic mechanism	The pro-erectile effect of F3-5 (the indole alkaloidal rich fraction from Aspidosperma ulei roots) when co-administered with haloperidol was evaluated. Mice were pre-treated with haloperidol (2 mg/kg, i.p.) 15 mins before the F3-5 injection (25 and 50 mg/kg). The result shows that haloperidol block the erectile effect induced by F3-5.	(Campos et al., 2006)

Table 5. Miscellaneous Haloperidol-HNPs Interactions on Animal Models (continued).

Types	Product	Model	Outcomes and findings			Reference
			Measurement	Mechanism	Effect	
HP	Asteracantha longifolia	Swiss albino rats	Erythropoietic activity↑	The presence of iron (622 µg/50 mg) in the extract may be contribute to the erythropoietic activity of the AL extract	The erythropoietic activity of Asteracantha longifolia Nees. (AL) on haloperidol induced iron deficiency anaemia was evaluated. The treatment group was given haloperidol (0.2 mg/kg, i.p.) along with ethanolic extract of AL (100 and 200 mg/kg, i.p.) for 4 days. Then haloperidol was withdrawn from all the extract treated groups and they were treated with their respective extract dose (100 and 200 mg/kg) continuously up to 15 days. Result showed that AL extract demonstrated a significant increase in erythrocyte count, haemoglobin count, serum iron and serum protein.	(Pawar et al., 2010)
HP	HU-210 (a cannabinoid CB1 agonist)	Male Sprague-Dawley rats	Immobility↑	The anti-depressant-like effect of CB1 receptor agonist, HU-210, is likely mediated by the activation of dopamine transmission	The effect of the haloperidol on the antidepressant-like effect of CB1 stimulation was studied in rats. The CB1 agonist HU-210 (0.1 mg/kg) and haloperidol (0.2 mg/kg) were administered before the forced swimming test. The result showed that haloperidol antagonized the antidepressant-like effect of HU-210.	(Sivrioglu et al., 2007)
HP	Withania somnifera	Albino mice	Immobility ∆	Dopaminergic receptors may not be involved in the immobility reducing effect of WS	The effect of antidepressant action of Withania somnifera (WS) and its interaction with haloperidol was evaluated in mice. Mice were pre-treated with haloperidol (0.1 mg/kg, i.p.) 60 min before forced swimming test while WS (100 mg/kg, i.p.) was administered 30 mins after haloperidol. A forced swimming test was used to evaluate the antidepressant activity. Result showed that haloperidol did not affect the effect of WS 100 mg/kg on duration of mean immobility time	(Demontis et al., 2011)
HP	Trichilia catigua	Non-fasted male Swiss mice	Immobility↓	The effects of TC probably involve the dopaminergic system, it may be linked to the activation of D3/D4 receptors since the effect is not modified by the selective D2 receptor antagonist pimozide.	The anti-immobility effects and possible mechanism of T. catigua (TC) extract was evaluated in mice. Mice were pre-treated with haloperidol (1 mg/kg, i.p.) 30 mins before the treatment with TC extract (200 mg/kg, p.o.) 6 h before testing. Result showed that the anti-immobility effect induced by TC extract were significantly reversed by haloperidol in the forced swimming model in mice.	(Campos et al., 2005)
HP	Scopoletin (isolated from Polygala sabulosa)	Female Swiss mice	Anti-depressant effect↓	The dopaminergic system may contribute to the anti-depressant-like effect of scopoletin.	The anti-depressant-like effect of scopoletin and its possible mechanism of action was investigated in the tail suspension test in mice. Mice were pre-treated with haloperidol (0.2 mg/kg, i.p.) 30 min before receiving scopoletin (10 mg/kg, p.o.) or vehicle. Tail suspension test was performed 60 min after. Result showed that co-administration of scopoletin with haloperidol block the antidepressant-like effect of scopoletin in the tail suspension test.	(Capra et al., 2010)

Table 5. Miscellaneous Haloperidol-HNPs Interactions on Animal Models (continued).

Types	Product	Model	Outcomes and findings			Reference
			Measurement	Mechanism	Effect	
HP	Niga-Ichigoside F1 (isolated from Rubus imperialis)	Swiss mice	Anti-nociception↓	The anti-nociceptive effect of Niga-Ichigoside (NI) may be related to the dopaminergic pathway	The anti-nociceptive effects of NI when co-administered with haloperidol was evaluated. Mice were pre-treated with haloperidol (0.2 mg/kg, i.p.) and were given NI (60 mg/kg, i.p.) to examine the antinociceptive action on formalin-induced nociception in mice. The time spent licking the injected paw was timed which serve as an indicator of pain. The first phase measures the nociceptive pain which is 5 min after formalin injection whereas the second phase measures the neurogenic and inflammatory pain which is 15–30 min after injection. Result showed that co-administration of haloperidol with NI significantly attenuate the antinociceptive effect by NI at both phases.	(Ardenghi et al., 2006)
HP	Morinda citrifolia Linn.	Sprague-Dawley male rats	Contractile response in isolated rat vas deferens preparations↓	Biphasic effect of on dopaminergic system	The results have demonstrated the biphasic effect of Morinda Citrifolia on dopaminergic system, with dopaminergic antagonistic effect at lower concentrations (<40 mg/mL) and dopaminergic agonistic effect at higher concentrations (>60 mg/mL).	(Pandy et al., 2014)
HP	Filicene (extracted from Adiantum cuneatum)	Male Swiss mice	Anti-nociception↓	The dopaminergic system may contribute to the anti-nociceptive effect of filicene. Co-administer with haloperidol, a non-selective dopaminergic antagonist will block the dopaminergic pathway and reduce the effect of filicene.	The possible mechanism of action of the antinociceptive property of filicene was investigated in mice. Mice were pre-treated with haloperidol (0.2 mg/kg, i.p.) followed 15 min later by filicene (30 mg/kg, i.p.) or apomorphine (1.0 mg/kg, i.p.). The analgesic effect was analysed 30 min after treatment with filicene and apomorphine. Result showed that pre-treatment with haloperidol reverses the antinociceptive effect caused by filicene, suggesting that anti-nociception is dependent on the dopaminergic system.	(De Souza et al., 2009)
HP	Catuama [2]	Wistar rats	Anti-nociception↓	The complete reversal of the anti-nociceptive effect of Catuama by haloperidol suggested that the anti-nociceptive effect of Catuama depends on the dopaminergic receptors or traditional pathways.	The anti-nociceptive effects of Catuama on mechanical allodynia induced by LPS was evaluated. Rats were pre-treated with haloperidol (1 mg/kg, i.p.), methysergide (1 mg/kg, i.p.) or yohimbine(1 mg/kg, i.p.) respectively. Catuama (200 mg/kg, p.o.) or saline 0.9% was given 1 h after. Result showed that anti-nociceptive effect of Catuama were reverted by pre-treatment with haloperidol. Neither methysergide nor yohmbine significantly affect the anti-nociceptive effects of Catuama.	(Quintao et al., 2008)
HP	Lithrea molleoides	Female Swiss mice	Anti-nociceptive effect↑	The dopaminergic system may involve in the antinociceptive action of LM extract. The anti-nociception possibly related to the presence of shikimic and avanillic acid.	The antinociceptive effect of Lithrea molleoides (LM) aqueous extract and its isolated compounds has been investigated in mice. Mice were pre-treated with haloperidol (1 mg/kg, i.p.) 30 mins before LM extract (10 mg/kg, i.p.). The nociceptive response was evaluated in the acetic acid-induced abdominal writhing test. Result showed that haloperidol enhanced the antinociceptive effect of LM.	(Morucci et al., 2012)
HP	Cedrus atlantica Essential Oil	Swiss mice	Depletion of norepinephrine	CAEO activated the descending pain modulation pathways on the opioidergic, serotonergic, noradrenergic and dopaminergic systems.	Cedrus atlantica essential oil (CAEO) alleviates postoperative pain. Inhalation of CAEO (5, 30 or 60 min) markedly reduced mechanical hypersensitivity. Haloperidol (1 mg/kg, i.p.) an antagonist of dopaminergic (D1 and D2) receptors prevented the effect of CAEO on hypersensitivity.	(Martins et al., 2015)

Table 5. Miscellaneous Haloperidol-HNPs Interactions on Animal Models (continued).

Types	Product	Model	Outcomes and findings			Reference
			Measurement	Mechanism	Effect	
HP	Sapogenin (from defatted seeds of Camellia oleifera)	Kunming mice	Dopamine level in striatum↑	Sapogenin activate dopamine receptor rather than adenosine receptor.	Sapogenin protected dopamine neurons through anti-neuroinflammation and activation of dopamine receptor, rather than adenosine receptor, and its amination improves its pharmacological effects.	(Ye et al., 2014)
HP	Muntingia calabura Leaves	mice and rat	Anti-nociception△	The anti-nociception effect of methanol extract of M. calabura (MEMC) was not cross talk with the dopaminergic pathway of haloperidol.	The MEMC was prepared in the doses of 100, 250 and 500 mg/kg. The MEMC, at all doses, demonstrated a significant dose-dependent antinociceptive activity in both the bradykinin- and phorbol 12-myristate 13-acetate (PMA)-induced nociception. 10 mg/kg atropine (a non-selective cholinergic receptor antagonist), 0.15 mg/kg prazosin (an α1-noradrenergic antagonist) and 20 mg/kg haloperidol (a non-selective dopaminergic antagonist) did not affect the extract's anti-nociception.	(Zakaria et al., 2014)
F	Ascorbic Acid	Adult Swiss mice	Immobility↑	The result suggested that the anti-immobility effect of ascorbic acid probably involves the dopaminergic system through an interaction with dopamine D2 receptors.	The effect of ascorbic acid in the tail suspension test and forced swimming test and its interaction with the monoaminergic system was investigated. Mice were pre-treated with haloperidol (0.2 mg/kg, i.p.) and received either the vehicle or ascorbic acid (0.1 mg/kg, i.p.) after 30 mins. The result shows that haloperidol prevented the anti-immobility effect of ascorbic acid in the TST.	(Binfare et al., 2009)
F	Vitamin E	Male adult Wistar rats	DA-super sensitivity behaviours↓	The effect of Vitamin E on tardive dyskinesia (TD) is possibly due to its properties as a potent free radical scavenger	The effect of vitamin E on haloperidol-induced TD was evaluated. The rats were given haloperidol (0.05 mg/kg/day, i.p.) for 30 days. The treatment group received concomitantly vitamin E rich food (400 mg/kg/day) started 3 weeks before the haloperidol treatment until the end of the trial. All groups were administered apomorphine (0.25 mg/kg, s.c.). Apomorpphine-induced behaviours were assessed: oral stereotypies, grooming and sitting. The result shows that Vitamin E significantly decrease in oral stereotypies and sitting behaviour. No significant effects were observed in grooming behaviour.	(Gattaz et al., 1993)
F	Saccharum officinarum	Male Wistar rats	Yawning and genital grooming↓	SO affect the neural circuits involved with yawning and genital grooming.	After administration of the aqueous extract of Saccharum officinarum (AE), the yawns and the genital grooming were quantified at 10 min intervals during 120 min. Since dopaminergic and cholinergic pathways are implied in these responses, AE were evaluated in the presence of haloperidol 0.5 mg/kg and atropine 2 mg/kg. AE 0.5 g/kg increased the yawns, effect that was blocked both by haloperidol and atropine.	(Gamberini et al., 2015)
F	Green Tea Extract	Rats	Fluid, food intake, growth rate↓, serotonergic metabolism↑, dopamine level↓	Haloperidol induced decreased dopamine was increased in the nucleus accumbent when co-administer with green tea extract (GTE).	For 6 weeks, rats were treated with water plus saline; GTE (1 g/L, p.o.) plus saline; water plus haloperidol (1 mg/kg, i.p.); and GTE (1 g/L, p.o.) plus haloperidol (1 mg/kg, i.p.), respectively. The results indicate that GTE potentiates haloperidol's effects, such as decreased fluid, food intake, and growth rate; increased anxiogenic behaviour; increased serotonergic metabolism; and decreased dopamine levels as compared to the water-drinking groups. However, the study does not indicate whether these findings are statistically significant.	(Malik and Haleem, 2012)

Note: [1] Contains: Cyperi Rhizoma, Paeoniae Radix Alba, Bupleuri Radix, Chuanxiong Rhizoma, Glycyrrhizae Radix Et Rhizoma, Aurantii Fructus, Citri Reticulatae Pericarpium; [2] Contains: Trichila Catigua, Paullinia Cupana, Ptychopetalum Olacoides and Zingiber Officinalis.
Abbreviation: N.D: not detected; TCM: traditional Chinses medicine; F: food and dietary supplements; HP: other herbal products; i.p.: intraperitoneal injection; p.o.: oral administration; i.v.: intravenous administration; s.c.: subcutaneous injection; i.m.: intramuscular injection TD: tardive dyskinesia; OD: orofacial dyskinesia.

3.5. Miscellaneous Interactions

Besides EPS and catalepsy related effects, there are 29 articles reported on interactions between haloperidol and TCM (4 articles), other herbal products (21 articles), and food and dietary supplements (4 articles) leading to other miscellaneous activities that were summarized in Table 5, including mainly anti-immobility effect, anti-depressant effect and other outcome measures such as sexual stimulating effect, erythropoietic activity, testosterone levels and hypothermic effect.

Administration of haloperidol significantly reversed the anti-immobility effect of ferulic acid, HU-210 (a cannabinoid CB1 agonist), Trichilia catigua, Polygala sabulosa, Salvia sclarea and ascorbic acid, suggesting that the anti-depressant like effects of these HNPs might involve the interaction with dopamine receptors (Binfare et al., 2009; Campos et al., 2005; Capra et al., 2010; Seol et al., 2010; Sivrioglu et al., 2007). On the other hand, lack of interaction with haloperidol in the immobility animal model indicates that the anti-immobility effect of Withania somnifera might not involve the activity of dopaminergic system (Demontis et al., 2011). In addition, the anti-nociceptive properties of the HNPs and their relationship with dopaminergic pathway have been examined. Three HNPs, niga-ichigoside F_1 obtained from Rubus imperialis (Rosaceae), Filicene obtained from Adiantum cuneatum and Catuama (consists of hydroalcoholic extracts from Trichila catigua, Paullinia cupana, Ptychopetalum olacoides and Zingiber officinalis) demonstrated a decrease in anti-nociception after co-administration with haloperidol, suggesting such effect might depend on dopaminergic pathway (Ardenghi et al., 2006; De Souza et al., 2009; Quintao et al., 2008). On contrary, the anti-nociceptive effect of Lithrea molleoides was reported to increase with the presence of haloperidol (Morucci et al., 2012).

4. Discussion

With the aim to provide guidance for healthcare professionals to identify potential interactions between haloperidol and HNPs, the current study systematically reviewed evidence from published literature. Based on the fact that utilization of haloperidol requires therapeutic drug monitoring, together with the increased popularity of HNPs, it is important for healthcare providers as well as other clinical/preclinical researchers to acquire comprehensive information on such interactions. In the current review, for the first time, we systematically summarized up-to-date evidence of interactions between haloperidol with HNPs from both pharmacokinetics and pharmacodynamics aspects in primary literature.

We classified the included studies into three categories including haloperidol-induced catalepsy models, EPS related interactions and miscellaneous interactions. Approximately 40% of findings from the included animal studies were on the haloperidol-induced catalepsy models on rats or mice, which focused on exploring certain properties of the studied HNPs. Another 24% of the included studies focused on EPS related interactions.

The current study only identified nine clinical trials, indicating lack of exploration of clinical utilization of haloperidol co-administration with HNPs. Among the nine clinical studies, three of them had high research qualities and low risk of bias, providing strong evidences on the enhanced antipsychotic effect of Ginkgo biloba co-treated with haloperidol. Other clinical trials, mostly open-labelled pilot studies, could also provide some hints on potential interactions between haloperidol and YGS, Kava extract WS 1490, and a supplement of ω-3 fatty acids, vitamin E and vitamin C. Other studies on herb-drug interaction with haloperidol were all pre-clinical, suggesting various mechanisms of herb-drug interaction of haloperidol. More attention should be received on these proposed mechanisms in further clinical studies.

It is observed that over 98% of the included reports are based on pharmacodynamics interactions and only two clinical trials (no animal study reported) studied the pharmacokinetics-based interactions of haloperidol. Although haloperidol is one of the anti-psychotic drugs that require careful monitoring in clinical practice, limited information was provided on changes in blood/brain concentration of haloperidol after administering HNPs. It is difficult to identify the nature of the summarized interactions without examining whether pharmacokinetic changes or pharmacodynamics interaction served as the leading role which was further illustrated as below:

- Haloperidol is mainly metabolized by CYP 3A4 (and CYP 2D6) in humans and similarly by CYP 3A in rodents (Avent et al., 2006; Igarashi et al., 1995). The CYP3A metabolism of haloperidol generates a pyridinium metabolite 4-(4-chlorophenyl)-1-[4-(4-fluorophenyl)-4-oxobutyl]pyridinium ion (HPP^+) (Bloomquist et al., 1994; Eyles et al., 1994). It is suggested that HPP^+ is responsible for the severe extrapyramidal side effects of haloperidol, including parkinsonism and tardive dyskinesia, by damaging neurons related to the extrapyramidal motor system (Kawashima et al., 2004; Usuki et al., 1998). The pyridinium metabolite is present in human brain, rat brain and mouse brain after administration of haloperidol and it accumulates in brain particularly after chronic administration (Crowley et al., 2013; Eyles et al., 1996; Igarashi et al., 1995). Since the HPP^+ levels that observed in rodent brain overlap the range of those detected in post-mortem human brains following chronic haloperidol treatment, these data from rodent study are relevant to humans (Crowley et al., 2013). It is reported that some first-generation antipsychotic drugs and their active metabolites have slow elimination from human brain, leading to accumulation of drugs and metabolites after

chronic treatment (Kornhuber et al., 2006). Therefore, to better understand the nature of interactions involving haloperidol, we would like to suggest that it is important to measure the blood concentrations or even brain concentrations at different brain regions relevant to the antipsychotic actions of both the parent drug haloperidol and its metabolite HPP^+ in the future interaction studies.

- On the other hand, haloperidol has high affinity dopamine D2-like receptors; however, it also possesses considerable affinity to other neurotransmitter receptors including sigma-1 receptor, alpha-1 adrenergic receptor and $5HT_{2A}$ serotoninergic receptor (Schotte et al., 1996). Therefore, the pharmacodynamics outcome from the interactions between haloperidol with HNPs might not be solely due to the interaction at dopaminergic transmissions. In order to identify the neurotransmitter system(s) involved in the interaction, receptor occupancy should be measured. Receptor occupancy refers to the percentage of available receptors bound to the compound of interest. It can be measured by in vivo or ex vivo methods by using a tracer that selectively bound to the receptor of interest (e.g. raclopride as a specific tracer for D2 receptor). For further details on the importance and methodology of receptor occupancy measurement, readers are referred to a recent review by Schotte et al. (Schotte et al., 1996). By comparing the receptor occupancy levels in the haloperidol-alone group, HNPs group and combination group after the behavioural assessments, the receptor(s) involved in the interaction could be identified and be correlated to the behavioural scores. Moreover, receptor occupancy level could provide insights on whether the haloperidol dose used in the animal study is relevant to human dose. Dopamine D2 receptor occupancy is a translatable biomarker: a therapeutic window of 60% to 80% D2 occupancy of antipsychotics in both rodents and humans (Uchida et al., 2011). Indeed, it is suggested that in many rodent studies the doses of antipsychotics (including haloperidol) administered are not comparable to those in humans, i.e. the receptor occupancy levels achieved in the animals are not comparable to those achieved in patients receiving chronic antipsychotic treatment (Kapur et al., 2003). Most commonly used dosage of haloperidol in animal models included in the current review is 1 mg/kg for both mice and rats, which, according to the U.S. Food and Drug Administration guidance (US Food and Drug Administration, 2005), equivalent to a human dose of 0.08–0.16 mg/kg, lower than the clinical recommended dosage for patients (0.16–0.33 mg/kg assuming patient with a body weight of 60 kg). Moreover, the dosage of haloperidol in articles exploring other outcomes various from 0.05 mg/kg on mice to 12 mg/kg on rats, equivalent to human dose of 0.008–1.92 mg/kg. In addition, majority of the animal experiments used intraperitoneal injection as the administration route while clinically haloperidol is most commonly given orally or intramuscularly. Such discrepancies in dosage and route of administration may limit the usefulness of these animal data in clinical practice. Variations in extraction methods of the herbs and lack of specific component list and dosage of each component in the studied formulae may also serve as barriers for reproducing the findings of the included articles. Thus, we would like to suggest using receptor occupancy level as guidance on future interaction study designing to provide more reflective evidence on the clinical practice.

Considering the long history and popularity of both haloperidol and HNPs, it is safe to assume that the number of articles identified by the current review is relatively small. Since the current review only covered search results from English databases, it is believed that more evidence might be found in publications in other languages. We conducted a pilot literature search of haloperidol-HNPs interactions in four Chinese databases in 2013, including Chinese BioMedical Literature Database, China Journal Net, Traditional Chinese Medical Database System, and Chinese Medical Academic Conference Database. A total 52 papers were identified in the preliminary key word search and a final of 14 papers were reviewed and considered relevant of the haloperidol-HNPs interactions, including 3 animal studies and 11 clinical trials. Among clinical studies, the haloperidol-HNPs interactions were studied in both adult and pediatric patients. Interestingly all 11 clinical studies reported beneficial effect on the combination use of haloperidol and HNPs. Among these clinical studies, ten of them were observational open-labelled studies without baseline outcome comparison reported, all with Jadad scale at 0 and high risk of bias. Only one double-blind randomized control trial (Jadad score: 4; risk of bias: some concerns) was found, reporting the beneficial effect of the artificial Calculus Bovis Sativus in the combination use with haloperidol on schizophrenic patients (Weng et al., 2010).

In order to gather as much information on the HNPs-haloperidol interaction, the current study included all identified articles regardless of the quality of the studies. However, with large numbers of animal studies and limited high-quality clinical reports identified, it is difficult to provide comprehensive clinical guidance on the haloperidol-HNPs interactions, especially potential adverse event. Other factors such as the herb authentication, extract method, dosage and dosage forms used varied among the articles also added on to the limitation of the current review. Regardless of the limitations, the current review not only is the first systematic summarizations of haloperidol-HNPS interactions but also provides insights and guidance in terms of future interaction study design. Both clinical healthcare

professionals and preclinical researchers can gather valuable information of the studied interactions from this review.

5. Conclusions

The current review is the first to provide systematically summarised evidence of interactions between haloperidol with HNPs. Such interactions were identified in both animal studies and clinical trials with major outcome measures such as change in level of catalepsy and EPS related symptoms. Healthcare professionals should be cautious while prescribing haloperidol along with HNPs, monitoring and communication with patients about the potential risk of interactions is advised. On the other hand, future preclinical interaction studies between HNPs and haloperidol should consider the pharmacokinetic and pharmacodynamic characteristics of haloperidol in order to obtain translatable information.

Acknowledgements

This study is supported by Hospital Authority of Hong Kong (Reference number: L/M (Q08-040) to HAHO(S)/P/ 45). The authors state no conflict of interest.

References

Aderibigbe AO, Iwalewa EO, Adesina SK, Adebanjo AO and Ukponmwan OE. Anticonvulsant, analgesic and hypothermic effects of aridanin isolated from Tetrapleura tetrapetra fruit in mice. J Boil Sci 2007; 7: 1520-1524.

Amoateng P, Adjei S, Osei-Safo D, Kukuia KK, Bekoe EO, Karikari TK et al. Extract of Synedrella nodiflora (L) Gaertn exhibits antipsychotic properties in murine models of psychosis. BMC Complement Altern Med. 2017b; 17: 389.

Amoateng P, Adjei S, Osei-Safo D, Kukuia KK, Karikari TK and Nyarko AK. An ethanolic extract of Desmodium adscendens exhibits antipsychotic-like activity in mice. J Basic Clin Physiol Pharmacol 2017a; 28: 507-518.

Ardenghi JV, Kanegusuku M, Niero R, Filho V, Monache FD, Yunesm RA, et al. Analysis of the mechanism of antinociceptive action of niga-ichigoside F1 obtained from Rubus imperialis (Rosaceae). J Pharm Pharmacol 2006; 58: 1669-1675.

Avent KM, DeVoss J and Gillam EM. Cytochrome P450-mediated metabolism of haloperidol and reduced haloperidol to pyridinium metabolites. Chem Res Toxicol 2006; 19: 914-920.

Badhe SR, Badhe RV, Ghaisas MM, Chopade VV and Deshpande AD. Evaluations of antidepressant activity of Anacyclus pyrethrum root extract. Int J Green Pharm 2010; 4.

Balderas JL, Reza V, Ugalde M, Guzman L, Serrano MI, Aguilar A, et al. Pharmacodynamic interaction of the sedative effects of Ternstroemia pringlei (Rose) Standl. with six central nervous system depressant drugs in mice. J Ethnopharmacol 2008; 119: 47-52.

Batool F, Shah AH, Ahmed SD and Haleem DJ. Oral supplementation of sea buckthorn (Hippophae rhamnoides L. spp. Turkestanica) fruit extract modifies haloperidol induced behavioral deficits and increases brain serotonin metabolism. J Food Drug Anal 2009; 17: 257-263.

Beasley C, Dellva MA, Tamura RN, Morgenstern H, Glazer WM, Ferguson K, et al. Randomised double-blind comparison of the incidence of tardive dyskinesia in patients with schizophrenia during long-term treatment with olanzapine or haloperidol. Br J Psychiatry 1999; 174: 23-30.

Beaubrun G and Gray GE. A review of herbal medicines for psychiatric disorders. Psychiatr Serv 2000; 51: 1130-1134.

Bhattacharya SK, Bhattacharya D and Sairam Ghosal S. Effect of Withania somnifera glycowithanolides on a rat model of tardive dyskinesia. Phytomedicine 2002; 9: 167-170.

Binfare RW, Rosa AO, Labato KR, Santos ARS and Rodrigues AL. Ascorbic acid administration produces an antidepressant-like effect: Evidence for the involvement of monoaminergic neurotransmission. Prog Neuropsychopharmacol Biol Psychiatry 2009; 33: 530-540.

Bloomquist J, King E, Wright A, Mytilineou C, Kimura K, Castagnoli K, et al. 1-Methyl-4-phenylpyridinium-like neurotoxicity of a pyridinium metabolite derived from haloperidol: cell culture and neurotransmitter uptake studies. J Pharmacol Exp Ther 1994; 270: 822-830.

Boerner RJ and Klement S. Attenuation of neuroleptic-indeuced extrapyramidal side effects by Kava special extract WS 1490. Wien Med Wochensche 2004; 154: 154-221.

Campos AR, Lima Jr. RCP, Uchoa DEA, Silveira ER, Santos FA and Rao VSN. Pro-erectile effects of an alkaloidal rich fraction from Aspidosperma ulei root bark in mice. J Ethnopharmacol 2006; 104: 240-244.

Campos MM, Fernandes ES, Ferreira J, Santos ARS, Calixto JB. Antidepressant-like effects of Trichilia catigua (Catuaba) extract: evidence for dopaminergic-mediated mechanisms. Psycho-pharmacology 2005; 182: 45-53.

Capra JC, Cunha MP, Machado DG, Zomkowski ADE, Mendes BG, Santos ARS, et al. Antidepressant-like effect of scopoletin, a coumarin isolated from Polygala sabulosa (Polygalaceae) in mice: Evidence for the involvement of monoaminergic systems. Eur J Pharmacol 2010; 643: 232-238.

Champatisingh D, Sahu PK, Pal A and Nanda GS. Anticataleptic and antiepileptic activity of ethanolic extract of leaves of Mucuna pruriens: A study on role of dopaminergic system in epilepsy in albino rats. Indian J Pharmacol 2011; 43: 197.

Cocka I. The safe usage of herbal medicines: counter-indications, cross-reactivity and toxicity. Phcog Commn 2015; 5: 2-50.

Colpo G, Trevisol F, Teixeira AM, Fachinetto R, Pereira RP, Athayde ML, et al. Ilex paraguariensis has antioxidant potential and attenuates haloperidol-induced orofacial dyskinesia and memory dysfunction in rats. Neurotox Res 2007; 12: 171-180.

Connor JD, Rostom A and Makonnen E. Comparison of effects of Khat extract and amphetamine or behaviours in mice. J Ethnopharmacol 2002; 81: 65-71.

Crowley JJ, Ashraf-Khorassani M, Castagnoli N and Sullivan PF. Brain levels of the neurotoxic pyridinium metabolite HPP+ and extrapyramidal symptoms in haloperidol-treated mice. Neuro-toxicology 2013; 39: 153-157.

Csernansky JG and Schuchart EK. Relapse and rehospitalisation rates in patients with schizophrenia. CNS Drugs 2002; 16: 473-484.

De Souza MM, Pereira MA, Ardenghi JV, Mora TC, Bresciani LF, Yunes RA, et al. Filicene obtained from Adiantum cuneatum interacts with the cholinergic dopaminergic, glutamatergic, GABAergic, and tachykinergic systems to exeert antinocicpetive effect in mice. Pharmacol Biochem Behav 2009; 93: 40-46.

Demontis F, Loi F, Malesa R, D'Aquila PS and Serra G. Antidepressant-like effect of cannabinoid CB1 receptor stimulation in the forced swimming test: the role of dopamine receptors. Int Clin Psychopharmacol 2011; 26: e41-e42.

Dorris RL and Dill RE. Potentiation of Haloperidol-induced Catalepsy by Ascorbic Acid in Rats and Nonhuman Primates. Pharmacol Biochem Behav 1986; 24: 781-783.

Eranti VS, Gangadhar BN and Janakiramaiah N. Haloperidol-induced extrapyramidal reaction: lack of protective effect by vitamin E. Psychopharmacology 1998; 140: 418-420.

Ernst E. Harmless herbs? A review of the recent literature. Am J Med 1998; 104: 170-178.

Eyles DW, McGrath JJ and Pond SM. Formation of pyridinium species of haloperidol in human liver and brain. Psychopharmacology 1996; 125: 214-219.

Eyles DW, McLennan HR, Jones A, McGrath JJ, Stedman TJ and Pond

SM. Quantitative analysis of two pyridinium metabolites of haloperidol in patients with schizophrenia. Clin Pharmacol Ther 1994; 56: 512-520.

Fachinetto R, Villarinho JG, Wagner C, Pereira RP, Ávila DS, Burger ME, et al. Valeriana officinalis does not alter the orofacial dyskinesia induced by haloperidol in rats: Role of dopamine transporter. Prog Neuro-Psychopharmacol Biol Psychiatry 2007; 31: 1478-1486.

Fang J, Baker GB, Silverstone PH and Coutts RT. Involvement of CYP3A4 and CYP2D6 in the metabolism of haloperidol. Cell Mol Neurobiol 1997; 17: 227-233.

Fong SYK, Gao Q and Zuo Z. Interaction of carbamazepine with herbs, dietary supplements, and food: a systematic review. J Evid Based Complementary Altern Med 2013; 2013.

Fong SYK, Wong YC and Zuo Z. Alterations in the CNS effects of anti-epileptic drugs by Chinese herbal medicines. Expert Opin Drug Metab Toxicol 2014; 10: 249-267.

Fontana L, Souza A, Del Bel E and Oliveira Rd. Ginkgo biloba leaf extract (EGb 761) enhances catalepsy induced by haloperidol and L-nitroarginine in mice. Braz J Med Biol Res 2005; 38: 1649-1654.

Fugh-Berman A. Herb-drug interactions. Lancet 2000; 355: 134-138.

Gadekar DH and Jitender K. Evaluation of anxiolytic activity of boerhaavia diffusa hydro-alcoholic extract of leaves in rats. International Research Journal of Pharmacy 2011; 2: 90-92.

Gamberini MT, Gamberini MC and Nasello AG. Involvement of dopaminergic and cholinergic pathways in the induction of yawning and genital grooming by the aqueous extract of Saccharum officinarum L.(sugarcane) in rats. Neurosci Lett 2015; 584: 270-275.

Gattaz WF, Emrich A and Behrens S. Vitamin E attenuates the development of haloperidol-induced dopaminergic hypersensitivity in rats: possible implications for tardive dyskinesia. J Neural Transm 1993; 92: 197-201.

Ghaisas M, Ninave P, Ganu G, Zope V, Tanwar M and Deshpande A. Effect of Randia dumetorum Lam on clonidine and haloperidol-induced catalepsy in mice. Pharmacologyonline 2008; 2: 42-50.

Girdhari LG and Avtar CR. Synergistic effect of Withania somnifera dunal and L-dopa in the inhiition of haloperidol-induced catalepsy in mice. Pharmacogn Mag 2009; 5: 46.

Gonçalves AE, Bürger C, Amoah SK, Tolardo R, Biavatti MW and de Souza MM. The antidepressant-like effect of Hedyosmum brasiliense and its sesquiterpene lactone, podoandin in mice: Evidence for the involvement of adrenergic, dopaminergic and serotonergic systems. Eur J Pharmacol 2012; 674: 307-314.

Granger B and Albu S. The haloperidol story. Ann Clin Psychiatry 2005; 17: 137-140.

Grzywacz JG, Suerken CK, Quandt SA, Bell RA, Lang W and Arcury TA. Older adults' use of complementary and alternative medicine for mental health: findings from the 2002 National Health Interview Survey. J Altern Complement Med 2006; 12: 467-473.

Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011; 343: d5928.

Howard N, Tsourounis C and Kapusnik-Uner J. Dietary supplement survey of pharmacists: personal and professional practices. J Altern Complement Med 2001; 7: 667-680.

Igarashi K, Kasuya F, Fukui M, Usuki E and Castagnoli N. Studies on the metabolism of haloperidol (HP): the role of CYP3A in the production of the neurotoxic pyridinium metabolite HPP+ found in rat brain following ip administration of HP. Life Sci 1995; 57: 2439-2446.

Ittiyavirah SP and Ruby R. Effect of hydro-alcoholic root extract of Plumbago zeylanica l alone and its combination with aqueous leaf extract of Camellia sinensis on haloperidol induced parkinsonism in wistar rats. Ann Neurosci 2014; 21: 47.

Izzo AA and Ernst E. Interactions between herbal medicines and prescribed drugs. Drugs 2001; 61: 2163-2175.

Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials 1996; 17(1): 1-2.

Jena M, Pal A, Mishra S and Mishra SS. Protective effect of Eclipta alba on haloperidol induced extrapyramidal movement disorders in albino rats. Indian J Pharmacol 2013; 45: S102.

Ka V, Ta G, Ra V, Ja N, Ma K, Pb V. Neuromodulatory effect of Acrous calamus leaves extract on dopaminergic system in mice. Int J PharmTech Res 2009; 1(4): 1255-1259.

Kane JM, Carson WH, Saha AR, McQuade RD, Ingenito GG, Zimbroff DL, et al. Efficacy and safety of aripiprazole and haloperidol versus placebo in patients with schizophrenia and schizoaffective disorder. J Clin Psychiatry 2002; 63: 763-771.

Kapur S and Mamo D. Half a century of antipsychotics and still a central role for dopamine D 2 receptors. Prog Neuropsychopharmacol Biol Psychiatry 2003; 27: 1081-1090.

Kapur S and Remington G. Dopamine D 2 receptors and their role in atypical antipsychotic action: still necessary and may even be sufficient. Biol Psychiatry 2001; 50: 873-883.

Kapur S, VanderSpek SC, Brownlee BA and Nobrega JN. Antipsychotic dosing in preclinical models is often unrepresentative of the clinical condition: a suggested solution based on in vivo occupancy. J Pharmacol Exp Ther 2003; 305: 625-631.

Kaushik D, Rani R, Kaushik P, Sacher D and Yadav J. In vivo and in vitro antiasthmatic studies of plant Piper longum Linn. Int J Pharmacol 2012; 8: 192-197.

Kawashima H, Iida Y, Kitamura Y and Saji H. Binding of 4-(4-chlorophenyl)-1-[4-(4-fluorophenyl)-4-oxobutyl] pyridinium ion (HPP+), a metabolite of haloperidol, to synthetic melanin: implications for the dopaminergic neurotoxicity of HPP+. Neurotox Res 2004; 6: 535-542.

Knable MB. Extract of Ginkgo biloba added to haloperidol was effective for positive symptoms in refractory schizophrenia. Evid Based Ment Health 2002; 5: 878-883.

Kornhuber J, Wiltfang J, Riederer P and Bleich S. Neuroleptic drugs in the human brain. Eur Arch Psychiatry Clin Neurosci 2006; 256: 274-280.

Kothari S, Minda M and Tonpay SD. Anxiolytic and antidepressant activities of methanol extract of Aegle marmelos leaves in mice. Indian J Physiol Pharmacol 2010; 54(4): 318-328.

Kudo S and Ishizaki T. Pharmacokinetics of haloperidol. Clin Pharmacokinet 1999; 37: 435-456.

Kuhn MA. Herbal remedies: drug-herb interactions. Crit Care Nurse 2002; 22: 22-32.

Kumar A and Kulkarni S. Effect of BR-16A (Mentat), a polyherbal formulation on drug-induced catalepsy in mice. Indian J Exp Biol 2006; 44(1): 45-48.

Lazzarini M, Salum C and Del Bel EA. Combined treatment of ascorbic acid or alpha-tocopherol with dopamine receptor antagonist or nitric oxide synthase inhibitor potentiates cataleptic effect in mice. Psychopharmacology 2005; 181: 71-79.

Lei K, He GF, Zhang CL, Liu YN, Li J, He GZ, et al. Investigation of the synergistic effects of haloperidol combined with Calculus Bovis Sativus in treating MK-801-induced schizophrenia in rats. Experimental Animals 2018; 67: 163-173.

MacLennan AH, Wilson DH and Taylor AW. The escalating cost and prevalence of alternative medicine. Preventive Medicine 2002; 35: 166-173.

Madhu A, Gupta G, Arali B, Chellappan DK and Dua K. Anti-Psychotic Activity of Aqueous Root Extract of Hemidesmus indicus: A Time Bound Study in Rats. Recent Pat Drug Deliv Formul 2017; 11: 36-41.

Mahadik S and Gowda S. Antioxidants in the treatment of schizophrenia. Medicamentos de actualidad 1996; 32: 553-565.

Mahadik S and Scheffer R. Oxidative injury and potential use of antioxidants in schizophrenia. Prostaglandins Leukot Essent Fatty Acids 1996; 55: 45-54.

Mahadik SP, Evans D and Lal H. Oxidative stress and role of antioxidant and ω-3 essential fatty acid supplementation in schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry 2001; 25: 463-493.

Mahajan SK, Chaudhari SK, Mahajan SK and Chaudhari SK. Evaluation of anti-asthmatic activity of Anacardium occidentale L. leaves. Pharmacologyonline 2011; 3: 449-455.

Maharudra SR, Amol K, Nilesh NA, Deepak NR and Sanjay RC. Anti-

cataleptic activity of the various extracts of Momordica dioica seed on clonidine and haloperidol. Pharmacologyonline 2011; 3: 592-600.

Malik T and Haleem D. Effects of Gree Tea Extreact (GTE) on Haloperidol (HAL) Induced Neuroleptic Anxiety Syndrome (NAS) and Parkinsonism in Rats. Parkinsonism Relat Disord 2012; 18: S231-S232.

Mamiya T and Nishimura A. Intake of fermented soybean (Natto) increased locomotor activity in mice. Biol Pharm Bull 2007; 30(4): 845-846.

Martins DF, Emer AA, Batisti AP, Donatello N, Carlesso MG, Mazzardo-Martins L, et al. Inhalation of Cedrus atlantica essential oil alleviates pain behavior through activation of descending pain modulation pathways in a mouse model of postoperative pain. J Ethnopharmacol 2015; 175: 30-38.

Matthews SC, Camacho A, Lawson K and Dimsdale JE. Use of herbal medications among 200 psychiatric outpatients: prevalence, patterns of use, and potential dangers. Gen Hosp Psychiatry 2003; 25: 24-26.

McIntyre RS, Brecher M, Paulsson B, Huizar K and Mullen J. Quetiapine or haloperidol as monotherapy for bipolar mania—a 12-week, double-blind, randomised, parallel-group, placebo-controlled trial. Eur Neuropsychopharmacol 2005; 15: 573-585.

Miyaoka T, Furuya M, Yasuda H, Hayashida M, Nishida A, Inagaki T, et al. Yi-gan san as adjunctive therapy for treatment-resistant schizophrenia: an open-label study. Clin Neuropharmacol 2009; 32: 6-9.

Moinuddin G, Devi K, Satish H and Khajuria DK. Comparative pharmacological evaluation of Hypericum perforatum and Rosmarinus officinalis for anti-depressant activity. Lat Am J Pharm 2011; 30: 1028-1032.

Momin R and Mohan M. Anxiolytic-Like Actions of Methanolic Extract of Solanum Torvum (Solanaceae) Seeds in Mice Pharmacologyonline 2011; 2: 1246-1256.

Morucci F, Lopez P, Mino J, Ferraro G and Gorzalczany S. Antinociceptive activity of aqueous extract and isolated compounds of Lithrea molleoides. J Ethnopharmacol 2012; 142: 401-406.

Nade V, Kawale L and Yadav A. Protective effect of Morus alba leaves on haloperidol-induced orofacial dyskinesia and oxidative stress. Pharm Biol 2010; 48: 17-22.

Nade V, Kawale L, Dwivedi S and Yadav A. Neuropharmacological evaluation of Hibiscus rosa sinensis roots in experimental animals. J Nat Remedies 2009; 9: 142-151.

Nade VS, Kawale LA, Zambre SS and Kapure AB. Neuroprotective potential of Beta vulgaris L. in Parkinson's disease. Indian J Pharmacol 2015; 47: 403.

Nagarjuna AP. Evaluation of antioxidant and antiparkinsonian activities of Brassica oleracea in haloperidol-induced tardive dyskinesia. Int J Green Pharm 2015; 9: 143-149.

Nagore D, Ghosh V and Patil M. Evaluation of antiasthmatic activity of Cassia sophera Linn. Pharmacogn Mag 2009; 5: 109.

Naidu P, Singh A and Kulkarni SK. Effect of Withania somnifera Root Extract on Haloperidol-induced orofacial dyskinesia: Possible Mechanism of Action. J Med Food 2003; 6: 107-115.

Nair V, Arjuman A, Gopalakrishna HN and Nandini M. Effect of Withania somnifera Root Extract on Haloperidol-induced Catalepsy in Albino Mice. Phytother Res 2008; 22: 243-246.

Narita Y, Satowa H, Kokubu T and Sugaya E. Treatment of epileptic patients with the Chinese herbal medicine 'Saiko-Keishi-To' (SK). IRCS J Med Sci 1982; 10(2): 88-89.

Nasri S, Oryan S, Rohani AH and Amin GR. The Effects of Vitex agnus castus Extract and its Interaction with Dopaminergic System on LH and Testosterone in Male Mice. Pak J Biol Sci 2007; 10: 2300-2307.

Nirmal S, Patel A, Bhawar S and Pattan S. Antihistaminic and antiallergic actions of extracts of Solanum nigrum berries: possible role in the treatment of asthma. J Ethnopharmacol 2012; 142: 91-97.

Nirmal SA, Dhasade VV, Shinde DC, Dighe NS, Pattan SR and Mandal SC. Anticataleptic effect of phyllanthus maderaspatensis linn leaves. Pharmacologyonline 2009; 3: 351-355.

Pandy V, Narasingam M, Kunasegaran T, Murugan DD and Mohamed Z. Effect of noni (Morinda citrifolia Linn.) fruit and its bioactive principles scopoletin and rutin on rat vas deferens contractility: an ex vivo study. The Scientific World Journal 2014; 2014.

Patil R, Dhawale K, Gound H and Gadakh R. Protective Effect of Leaves of Murraya koenigii on Reserpine-Induced Orofacial Dyskinesia. Iran J Pharm Res 2012; 11: 635-641.

Patil R, Hiray Y, Shinde S and Langade P. Reversal of haloperidol-induced orofacial dyskinesia by Murraya koenigii leaves in experimental animals. Pharm Biol 2012; 50: 691-697.

Pawar RS, Jain AP, Lodhi S and Singhai AK. Erythropoietic activity of Asteracantha longifolia (Nees.) in rats. J Ethnopharmacol 2010; 129: 280-282.

Perry R, Campbell M, Adams P, Lynch N, Spencer EK, Curren EL, et al. Long-term efficacy of haloperidol in autistic children: continuous versus discontinuous drug administration. J Am Acad Child Adolesc Psychiatry 1989; 28: 87-92.

Pingale T and Prabhavalkar K. Antiparkinsonian effects and mechanistic insights of some indigenous herbal formulations. Int J Pharm Sci Res 2015; 6: 4760-4771.

Quintao NLM, Ferreira J, Beirith A, Campos MM and Calixto JB. Evaluation of the effects of the herbal product Catuama in inflammatory and neuropathic models of nociception in rats. Phytomedicine 2008; 15: 245-252.

Rao NV, Pujar B, Nimbal S, Shantakumar S and Satyanarayana S. Nootropic activity of tuber extract of Pueraria tuberosa (Roxb). Indian J Exp Biol 2008; 46: 591.

Rasheed A, Venkataraman S, Jayaveera K, Fazil AM, Yasodha K, Aleem M, et al. Evaluation of toxicological and antioxidant potential of Nardostachys jatamansi in reversing haloperidol-induced catalepsy in rats. Int J Gen Med 2010; 3: 127.

Rasheed AS, Venkataraman S, Fazil AM and Jayveera KN. Evaluation of antioxidant potential of smilax zeylanica linn. in reversing haloperidol induced catalepsy in rats. J Pharm Pharm Sci 2012; 4: 323-327.

Rasheed AS, Venkataraman S, Jayaveera KN, Mohammed FA, Mohammed I and Krishna Y. Effect of hydro-alcoholic root extract of Nardostachys jatamansi on haloperidol induced Parkinsonism in Wistar rats. Pharmacologyonline 2009; 2: 1145-1154.

Rathbone J, Zhang L, Zhang M, Xia J, Liu X and Yang Y. Chinese herbal medicine for schizophrenia. The Cochrane Library, 2005.

Rathbone J, Zhang L, Zhang M, Xia J, Liu X, Yang Y, et al. Chinese herbal medicine for schizophrenia. Br J Psychiatry 2007; 190: 379-384.

Reddy MV and Singhal M. Evaluation of Anti-Parkinsonian activity of seed extract of Nelumbo Nucifera. Int J Pharm Bio Sci 2014; 5: 469-485.

Reddy RD and Yao JK. Free radical pathology in schizophrenia: a review. Prostaglandins Leukot Essent Fatty Acids 1996; 55: 33-43.

Reynolds GP. Receptor mechanisms in the treatment of schizophrenia. J Psychopharmacol 2004; 18: 340-345.

Saeedi H, Remington G and Christensen BK. Impact of haloperidol, a dopamine D 2 antagonist, on cognition and mood. Schizophr Res 2006; 85: 222-231.

Sardjono RE, Khoerunnisa F, Musthopa I, Khairunisa D, Suganda PA and Rachmawati R. Synthesize of zinc nanoparticles using Indonesian velvet bean (Mucuna pruriens) extract and evaluate its potency in lowering catalepsy in mice. IOP Conf Ser: Mater Sci Eng 2018; 299: 012080.

Sathya B. Psychopharmacological evaluation of ethanolic extract of leaves of Bauhenia taumentosa L. in mice. International Journal of Pharmacy and Technology 2011; 3: 3693-3709.

Schotte A, Janssen P, Gommeren W, Luyten W, Van Gompel P, Lesage A, et al. Risperidone compared with new and reference antipsychotic drugs: in vitro and in vivo receptor binding. Psychopharmacology 1996; 124: 57-73.

Seol GH, Shim HS, Kim PJ, Moon HK, Lee KH, Shim I, et al. Antidepressant-like effect of Salvia sclarea is explained by modulation of dopamine activities in rats. J Ethnopharmacol 2010; 130: 187-190.

Shaik RA, Ahemad R, Venkataraman S and Jayaveera KN. Anti-oxidant

and anti-cataleptic activity of smilax zeylanica linn. J Clin Psychopharmacol 2012; 18: S45.

Shapiro E, Shapiro AK, Fulop G, Hubbard M, Mandeli J, Nordlie J, et al. Controlled study of haloperidol, pimozide, and placebo for the treatment of Gilles de la Tourette's syndrome. Arch Gen Psychiatry 1989; 46: 722-730.

Singh V, Singh SP and Chan K. Review and meta-analysis of usage of ginkgo as an adjunct therapy in chronic schizophrenia. Int J Neuropsychopharmacol 2010; 13: 257-271.

Sivrioglu EY, Kirli S, Sipahioglu D, Gursoy B and Sarandol E. The impact of omega-3 fatty acids, vitamins E and C supplementation on treatment outcome and side effects in schizophrenia patients treated with haloperidol: An open-label pilot study. Prog Neuropsychopharmacol Biol Psychiatry 2007; 31: 1493-1499.

Someya T, Shibasaki M, Noguchi T, Takahashi S and Inaba T. Haloperidol metabolism in psychiatric patients: importance of glucuronidation and carbonyl reduction. J Clin Psychopharmacol 1992; 12: 169-174.

Straw GM, Bigelow LB and Kirch DG. Haloperidol and Reduced Haloperidol Concentrations and Psychiatric Ratings in Schizophrenic Patients Treated with Ascorbic Acid. J Clin Psychopharmacol 1989; 9: 130-132.

Sudhakar Pemminati, V Nair, Dorababu P, Gopalakrishna HN and Pai Mrsm. Effect of Aqueous Fruit Extract of Emblica Officinalis on Haloperidol Induced Catalepsy in Albino Mice. J Clin Diagn Res 2009; 3: 1657-1662.

Tamilanban T, Manasa K, Raju D and Chitra V. Effect of methanolic extract of canscora decussate on haloperidol—Induced motor deficits in albino mice. Int J Pharm Sci Rev Res 2015; 35: 7-11.

Taur D, Nirmal S and Patil R. Effect of various extracts of Ficus bengalensis bark on clonidine and haloperidol-induced catalepsy in mice. Pharmacologyonline 2007; 3: 470-477.

Thaakur S and Hummabindhu G. Effect of alpha lipoic acid on the tardive dyskinesia and oxidative stress induced by haloperidol in rats. J Neural Transm 2009; 116: 807-814.

Thaakur S and Jyothi B. Effect of Spirulina maxima on the haloperidol induced tardive dyskinesia and oxidative stress in rats. J Neural Transm 2007; 114: 1217-1225.

Tote M, Mahire N, Jain A, Bose S, Undale V and Bhosale A. Effect of Ageratum conyzoides Linn on clonidine and haloperidol induced catalepsy in mice. Pharmacologyonline 2009; 2: 186-194.

Trevizol F, Benvegnú DM, Barcelos RC, Pase CS, Segat HJ, Dias VT, et al. Comparative study between two animal models of extrapyramidal movement disorders: prevention and reversion by pecan nut shell aqueous extract. Behav Brain Res 2011; 221: 13-18.

US Food and Drug Administration. Guidance for industry: estimating the maximum safe starting dose in initial clinical trials for therapeutics in adult healthy volunteers. Center for Drug Evaluation and Research (CDER), 2005.

Uchida H, Takeuchi H, Graff-Guerrero A, Suzuki T, Watanabe K and Mamo DC. Dopamine D2 receptor occupancy and clinical effects: a systematic review and pooled analysis. J Clin Psychopharmacol 2011; 31: 497-502.

Ulrich S, Wurthmann C, Brosz M and Meyer FP. The relationship between serum concentration and therapeutic effect of haloperidol in patients with acute schizophrenia. Clin Pharmacokinet 1998; 34: 227-263.

Usuki E, Van Der Schyf CJ and Castagnoli Jr N. Metabolism of haloperidol and its tetrahydropyridine dehydration product HPTP. Drug Metab Rev 1998; 30: 809-826.

Viana AF, Maciel IS, Motta EM, Leal PC, Pianowski L, Campos MM, et al. Antinociceptive activity of Trichilia catigua hydroalcoholic extract: new evidence on its dopaminergic effects. J Evid Based Complementary Altern Med 2011; 2011: 120820.

Vyawahare N and Bodhankar S. Neuropharmacological profile of Piper betel leaves extract in mice. Pharmacology online 2007; 2: 146-162.

Warcho P, Wankeu-nya M, Nguelefack TB, Tapondjou L, Teponno R and Kamanyi A. Pro-sexual Effects of Dracaena arborea (wild) link (Dracaenaceae) and sexually experienced male rats. Pharmacologyonline 2007; 1: 400-419.

Weng SH, Wang GH and Wang XP. A randomized double-blinded controlled study on treatment of schizophrenia by in vitro fostered bezoar combined with haloperidol. Zhongguo Zhong Xi Yi Jie He Za Zhi = Chinese journal of integrated traditional and Western medicine 2010; 30: 1213.

Wyosky D and Baum C. Antipsychotic drug use in the United States. Arch Gen Psychiatry 1989; 46: 929-932.

Yadav AV and Nade VS. Anti-dopaminergic effect of the methanolic extract of Morus alba L. leaves. Indian J Pharmacol 2008; 40: 221.

Yasui N, Kondo T, Suzuki A, Otani K, Mihara K, Furukori H, et al. Lack of significant pharmacokinetic interaction between haloperidol and grapefruit juice. Int Clin Psychopharmacol 1999; 14: 113-118.

Ye Y, Fang F and Li Y. Isolation of the sapogenin from defatted seeds of Camellia oleifera and its neuroprotective effects on dopaminergic neurons. J Agric Food Chem 2014; 62: 6175-6182.

Zakaria ZA, Sani MH, Cheema MS, Kader AA, Kek TL and Salleh MZ. Antinociceptive activity of methanolic extract of Muntingia calabura leaves: further elucidation of the possible mechanisms. BMC Complement Altern Med 2014; 14: 63.

Zhang XY, Zhou DF, Cao LY and Wu GY. The effects of Ginkgo biloba extract added to haloperidol on peripheral T cell subsets in drug-free schizophrenia: a double-blind, placebo-controlled trial. Psychopharmacology (Berl) 2006; 188: 12-17.

Zhang XY, Zhou DF, Su JM and Zhang PY. The effect of extract of ginkgo biloba added to haloperidol on superoxide dismutase in inpatients with chronic schizophrenia. J Clin Psychopharmacol 2001b; 21: 85-88.

Zhang XY, Zhou DF, Zhang PY, Wu GY, Su JM and Cao LY. A double-blind, placebo-controlled trial of extract of Ginkgo biloba added to haloperidol in treatment-resistant patients with schizophrenia. J Clin Psychiatry 2001a; 62: 878-883.

Zhang Y, Huang X, Wang Y, Xie Y, Qiu X, Ren P, et al. Ferulic acid-induced anti-depression and prokinetics similar to Chaihu–Shugan–San via polypharmacology. Brain Res Bull 2011c; 86: 222-228.

Zhang ZJ, Tan QR, Tong Y, Wang XY, Wang H-H, Ho LM, et al. An epidemiological study of concomitant use of Chinese medicine and antipsychotics in schizophrenic patients: implication for herb-drug interaction. PLoS One 2011; 6: 17239.

Zhang ZJ, Tan QR, Zhen XC and Tong Y. The potential benefits of herbal medicines for schizophrenia: from empirical observations to clinical trials. Clinical Trials in Psychopharmacology 2010; 16: 311-335.

Supplementary Table 1. PRISMA Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Page 1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Page 2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Page 3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Page 3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Page 4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Page 4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Page 3
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Table 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Figure 1
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Page 4
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Not applicable
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Page 4
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Not applicable
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Not applicable

Supplementary Table 1. PRISMA Checklist (continued)

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Page 4
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Not applicable
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Page 6 Table 2-5
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Page 4 Table 4
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Page 4-6
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Not applicable
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Page 4 Table 4
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Not applicable
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Page 7
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Page 8
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Page 8
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Page 8

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.