Systematic Review of Polyherbal Combinations Used in Metabolic Syndrome

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Background: Metabolic syndrome (MetS) is a multifactorial disease, whose main stay of prevention and management is life-style modification which is difficult to attain. Combination of herbs have proven more efficacious in multi-targeted diseases, as compared to individual herbs owing to the “effect enhancing and side-effect neutralizing” properties of herbs, which forms the basis of polyherbal therapies This led us to review literature on the efficacy of herbal combinations in MetS.

Methods: Electronic search of literature was conducted by using Cinnahl, Pubmed central, Cochrane and Web of Science, whereas, Google scholar was used as secondary search tool. The key words used were “metabolic syndrome, herbal/poly herbal, metabolic syndrome, clinical trial” and the timings were limited between 2005–2020.

Results: After filtering and removing duplications by using PRISMA guidelines, search results were limited to 41 studies, out of which 24 studies were evaluated for combinations used in animal models and 15 in clinical trials related to metabolic syndrome. SPICE and SPIDER models were used to assess the clinical trials, whereas, a checklist and a qualitative and a semi-quantitative questionnaire was formulated to report the findings for animal based studies. Taxonomic classification of Poly herbal combinations used in animal and clinical studies was designed.

Conclusion: With this study we have identified the potential polyherbal combinations along with a proposed method to validate animal studies through systematic qualitative and quantitative review. This will help researchers to study various herbal combinations in MetS, in the drug development process and will give a future direction to research on prevention and management of MetS through polyherbal combinations.

Keywords: obesity, natural products, clinical trials, animal models, polyherbal
INTRODUCTION

Non-communicable diseases (NCDs) account for 71% of the deaths worldwide with rising prevalence in lower- and middle-income countries (Huang, 2009; Robinson et al., 2013). NCDs have been ranked as one of the top ten global threats in 2019 by World Health Organization (Khowaja et al., 2017; Robinson et al., 2013). Metabolic syndrome (MetS) is a type of NCD with worldwide prevalence ranging from less than 10% to as much as 84% (Rhee et al., 2010) with the burden being greater in South Asian countries (Sever et al., 2003; Su and Li, 2011).

MetS is characterized by a cluster of three or more features including hyperglycaemia, hypertriglyceridaemia, a low level of high-density lipoprotein cholesterol (HDL-C), blood pressure and central obesity (Bodeker and Kronenberg, 2002; Anderson and Taylor, 2012). A person who has at least three out of five of these characteristics is labelled as MetS patient. The following criteria should be met for MetS (AuH, 1998; Anderson and Taylor, 2012): waist circumference more than 35 and 40 inches in women and men, respectively (central obesity); triglycerides (TGs) 150 mg/dl or greater, HDL-C less than 50 and 40 mg/dl in women and men, respectively, blood pressure (BP) of 130/85 mm Hg or higher, fasting blood glucose (FBG) of 100 mg/dl or greater. Besides the above mentioned abnormalities, underlying initiators of MetS are inflammation, oxidative stress and insulin resistance (Ma et al., 2009; Aziz et al., 2013; Amin et al., 2015a). Together these factors pose a three- and five-fold greater risk for cardiovascular disease (CVD) and type II diabetes mellitus (T2DM) respectively (Zimmermann et al., 2007), along with high mortality rate (Gilani and Rahman, 2005).

MetS has multiple aetiologies and therefore no single drug can be effective in reversing this situation. The mainstay of prevention and management of individuals at risk is lifestyle modification. However, those who have high levels of risk factors are the recipients for pharmacological treatment which is aimed towards individual symptoms’ management (AuH, 1998; Devalaraja et al., 2011; Mohamed, 2014). Multiple drugs including drugs to lower the blood glucose level, TGs, and blood pressure (Robinson et al., 2013) may be needed for a long time resulting in drug-related complications, low compliance rate and high cost of care (Khawaja et al., 2007; Huang, 2009). Alternately, some researchers suggest to advocate life-style modification as the first line therapy for prevention of a chronic disease, rather than using pharmacological therapies such as metformin in pre-diabetes (Rhee et al., 2010) and statins in mild to moderate dyslipidemia (Sever et al., 2003). Endorsing only lifestyle modifications is challenging for the physicians especially among high-risk patients such as in obese patients, since compliance to dietary modification, and physical activity is difficult to attain (Samir et al., 2011). Therefore, it is imperative to explore innovative therapies which are cost-effective and acceptable, with fewer adverse effects, in order to reduce the risk of cardiovascular diseases (CVD) through addressing the risk factors.

According to World Health Organization (WHO), up to 80% of the Asian population relies on complementary and alternative/Traditional medicine (CAM/T) for their primary healthcare, possibly because more than 80% of people in developing nations can barely afford basic medical needs (Su and Li, 2011). Interestingly, almost half of the population in the developed world also uses CAM/T therapies (Bodeker and Kronenberg, 2002). Amongst the most common complementary modalities used by individuals with CVD risk factors are natural products (Anderson and Taylor, 2012) that have evidently contributed in the development of modern medicine for cardiovascular disorders (AuH, 1998). MetS requires multiple factors to be addressed simultaneously, therefore polyherbal combinations can offer a safe and more effective therapeutic option. Research has revealed that the multi-component properties of polyherbal combinations make them suitable for treating complex diseases and offer great potential for exhibiting synergistic actions. Evaluation of literature from individual effects of potential polyherbal combinations paves the path for deriving new combinations.

Synergistic therapeutic actions of polyherbal formulations are possible through underlying mechanisms such as regulation of same or different targets in various pathways hence in combination enhance efficacy, regulation of enzymes and transporters to improve oral drug bioavailability, neutralize adverse effects and overcome drug resistance mechanisms. Synergism is observed when multiple chemical constituents are present in single or in combination of herbs (Amin et al., 2015a), which are potential therapeutic options for various disease targets. This forms the basis of polyherbal therapies (Ma et al., 2009; Aziz et al., 2013) and is considered rational and more efficacious in multi-targeted diseases (Zimmermann et al., 2007). The effect-enhancing and side-effect neutralizing properties of polyherbal combinations (Gilani and Rahman, 2005) prompted us to review the literature on the efficacy of polyherbal combinations in metabolic syndrome, the incidence of which is rising globally. This will help researchers to identify various effective polyherbal combinations in MetS, which may help in the drug development process, as well as provide future direction towards research on prevention and cure of a menace like metabolic syndrome. Although synergistic therapeutic interactions of herbal ingredients have been frequently reported, to the best of our knowledge, none of the reports have offered review of polyherbal formulations in MetS. Individual herb reviews related to MetS were limited to functional foods (Mohamed, 2014) and exotic fruits (Devalaraja et al., 2011). Hence, in this review, we present recent literature reporting herb synergisms and efficacy of various polyherbal formulations in MetS. We have identified the herb to be good if it manages to modulate at least 3 out of 5 MetS criteria.

METHODS

Systematic Review Protocol (Search Strategy and Data Sources)

We decided for a qualitative systematic review for which an electronic literature search was carried out to find articles published mainly in the last 15 years (2005–2020).
For this purpose, following databases, and/or search engines were used: Cinnahl, Pubmed central, Cochrane, Web of Science and Scopus. Google scholar was used as secondary search tool. The key words used were “metabolic syndrome, herbal/polyherbal,” “metabolic syndrome, clinical trial”.

**Inclusion Criteria**
1. Animal model with MetS that are given more than one herb for treatment.
2. Adults diagnosed with MetS (who qualify for 3 of the 5 MetS parameters: obesity, high blood pressure,
### TABLE 1 | Taxonomic classification of all the polyherbal combinations reviewed in animal Studies.

| S.No | Reference | Name of the Combination | Components | Chinese Name | Common name | Scientific name | Family | Specie |
|------|-----------|--------------------------|------------|--------------|--------------|----------------|--------|--------|
| 1    | Thota et al. (2014) | Dhaekseunggitiang | Curcuma longa (Rhizomes), Salacia reticulata (Root), Gymnema sylvestre (leaves), Emblica officinalis (fruits), Terminalia chebula (fruits) | Turmeric, Kotalis himbutu | Curcuma longa L., Salacia reticulata, Wight Gymnema sylvestre (Retz.) Schult Emblica officinalis Gaertn., Phyllanthus emblica, L. Terminalia chebula Retz. | Zingiberaceae | C. longa |
| 2    | Sung et al. (2014) | Dohaekseunggitiang | Glycyrrhiza uralensis Fischer (40 g), Rheum undulatum Linne (80 g), Prunus persica Linne (60 g), Cinnamomum cassia Presl (40 g), and Natrii Sulfas (40 g) | Chinese licorice root | Glycyrrhiza uralensis, Fisch. ex DC Rheum undulatum Linne; Rheum rhubarbarum L Prunus persica (L) Batsch | Polygonaceae | R. undulatum; R. rhubarbarum |
| 3    | Li et al. (2013) | Huang-Lian-Jie-Du-Tang | Rhizoma Coptidis, Radix Scutellariae, Cortex Phellodendri and Fructus Gardeniae (3:2:2:2:3) | Chinese goldthread or canker root | Coptis chinensis Franch; Coptis deltoidea C.Y. Cheng et Hsiao, and Coptis teeta Wall Scutellaria baicalensis, Georgi Phellodendron amurense or Phellodendron chinense | Ranunculaceae | C. chinensis; C. deltoidea and C. teeta |
| 4    | Kho et al. (2018) | RGPM: | Red ginseng and Polygoni Multiflori Radix (1:1) | Chinese climbing knotweed | Gardenia; Cape Jasmine Red ginseng (produced by steaming and drying fresh and raw ginseng) | Rubiaceae | G. jasminoides |
| 5    | Yao et al. (2017b) | Modified lingguizhugan decoction | Poria cocos Wolf, Cinnamomum cassia Presl, Atractylodes lancea DC., Glycyrrhiza uralensis Fisch., Nanf. and Rheum palmatum L] (ratio of 12:9:6:6:9:9) | Wolfiporia cocos (F.A. Wolf) Ryvarden and Gilb., Cinnamomum cassia (L.) Presl Atractylodes lancea (Thunb) DC Glycyrrhiza uralensis, Fisch Rheum palmatum | Polygonaceae | P. multiflorum, R. multiflora |
| 6    | Amin et al. (2015a) | Curcuma longa and Nigella Sativa | Turmeric | Curcuma longa L. | Curcuma longa L. | Zingiberaceae | C. longa |

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| S.No | Reference            | Name of the Combination                                      | Components                                                                 | Chinese Name | Common name                      | Scientific name | Family            | Specie                  |
|------|----------------------|---------------------------------------------------------------|----------------------------------------------------------------------------|--------------|----------------------------------|------------------|---------------------|-------------------------|
| 7    | Mounts et al. (2015) | soybean meal and probiotics (Bifidobacterium, longum (BB536)) | Mung bean; Soybean meal                                                   |              | Vigna radiata, (L.) R. Wilczek, | Fabaceae         | V. radiata, T. glycinis |
| 8    | Lee et al. (2015b)   | ACE                                                           | Probiotics (BB536)                                                         |              | Bifidobacterium longum Reuter 1963 | Pastorisaceae   | B. longum           |
| 9    | Hu et al. (2014)     | Zhu Tiao Zhi formula (FT2)                                    | Turmeric; Chinese Privet; Glossy privet; Blaizhu (rhizome)                 |              | Curcuma longa L, Ligustrum lucidum, W.T. Alton | Zingiberaceae | C. longa            |
|      |                      |                                                               | Red sage; Chinese sage                                                     |              | Atractylodes macrocephala Koidz. | Compositae/ Asteraceae | A. macrocephala     |
| 10   | Gao et al. (2015)    | Erchen decoction                                              | Pericarpium of mandarin orange (dried and ripe peel)                       |              | Citrus medica var, sarcodactylus | Rutaceae        | P. nigrum           |
| 11   | Kaur and C (2012)    | CPQ                                                           | Curcumin (pure chemical from turmeric)                                    |              | Curcuma longa L                  | Piperacea        | P. nigrum           |
| 12   | Tan et al. (2013)    | Erchen decoction                                              | Danahen                                                                     |              | Plant flavonol from the flavonoid group of polyphenols | Lamiaceae | S. miltiorrhiza    |
| 13   | Wei et al. (2012)    | SUB885C                                                       | Fructus Crataegi, Folium Nelumbinis, Folium Apocyni, Flos                   |              | Gardenia jasminoides, J.Ellis    | Rosaceae        | C. monogyna          |
|      |                      |                                                               | Gardenia; Cape Jasmine                                                     |              | Lotus leaf                        | Nelumbonaceae    | N. nuclera          |
|      |                      |                                                               | He ye herb                                                                   |              | Sword-leaf dogbane (Folium Apocyni) | Nymphaeaceae    | A. venetum          |

(Continued on following page)
| S.No | Reference | Name of the Combination | Components | Chinese Name | Common name | Scientific name | Family | Specie |
|------|-----------|-------------------------|------------|--------------|-------------|----------------|--------|--------|
| 14   | Azushima et al. (2013) | Bofu-tsu-shosan | Glycyrrhizae radix, Schizonepetae spica, Ephedrae herba, Forsythiae fructus, Others: | Fried Radix, Glycyrrhizae | Beach rose Radix et Rhizoma Rhei; Chinese rhubarb; Rheum | Apocynum venetum, L. Rosa rugose, Thunb. Rheum palatum L., Rheum tanguticum Maxim. ex Balf., and Rheum officinalis Bailey | Rosaceae | R. rugosa, R. palmatum, R. tanguticum, and R. officinalis |
|      |           | Jing jie                | Glycyrrhizae radix; Liquorice root; Glycyrrhiza radix; Liquorice root; Schizonepetae spica; Japanese catnip | Haidao Gau | Ephedrae herba; Joint-pine, jointfr, Mormon-tea or Brigham tea | Sargassum pallidum (Turner) C. Agardh Glycyrrhiza uralensis, Fisch Glycyrrhiza uralensis, Fisch | Fabaceae | G. uralensis, G. uralensis |
|      |           | Ianaqiao                | Weeping forsythia ; golden-bell Forsythia fructus (fruit of Forsythia suspense) | Hai Zao (HZ) | Schizonepeta tenuifolia (Benth.) Briq; Nepeta tenuifolia Benth | Ephedra sinica Stapf | Lamiaceae | S. tenuifolia |
|      |           | Duan Shao               | Chinese bellflower root; balloon flower root; Platycodi radix (the root of Platycodon main component: CaSO₄, Atractylodes rhizome Rhei rhizome; Chinese rhubarb; Rheum | Duan Shao | Platycodon grandifloras (Jacq) A. DC Atractylodes macrocephala Atractylodes macrocephala Koidz. | A. macrocephala | Campanulaceae | P. grandiflorum |
|      |           | Da Huang                | Chinese bellflower root; balloon flower root; Platycodi radix (the root of Platycodon main component: CaSO₄, Atractylodes rhizome Rhei rhizome; Chinese rhubarb; Rheum | Baikal | Rheum palatum L. | Lamiaceae | P. grandiflorum |
|      |           | Zhizi                   | Gardenia; Cape Jasmine Paeoniae radix; Peony root; Chinese peony dried root stem of Cnidium officinale; cnidii rhizome | Zhizi | Scutellaria baicalensis, Georgi Gardenia jasminoides, J.Ellis Paeonia lactiflora Pall | Rubiaceae | G. jasminoides, P. lactiflora |
|      |           | Duhuo                  | Angelicae radix | Duhuo | Cnidium officinale Makino; Lipisticum officinale (Makino) Kitag. | A. pubescens | Apiaceae | A. pubescens |
|      |           | Bo He Fang feng         | Menthae herba Radix Ledebouriella Ginger (Zingiberis rhizome) | Bo He Fang feng | Angelica pubescens Maxim. Mentha canadensis L.; Menthae haplocalyx Briq | Lamiaceae | M. Haplocalyx, S. divaricata |

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| S.No | Reference       | Name of the Combination | Chinese Name | Common Name | Scientific name | Family | Species |
|------|-----------------|-------------------------|--------------|-------------|-----------------|--------|---------|
| 15   | Li et al. (2015) | Tang-Nai-Kang: Fructus Ligustri Lucidi, Spica Prunellae vulgaris, Psidium guajava, and Radix ginseng (25:10:10) | Nuzhenzi      | Oligosaccharidova divaricata (Turcz.) Schischk; Ledebouriella divaricata (Turcz.) Hiroe | Lamiaceae | P. vulgaris |
| 16   | Chen et al. (2017) | Wendan decoction (WDD): Radix Glycyrrhizae (3 g), Pericarpium Citri Reticulatae (9 g), Poria Cocos (4.5 g), Citrus aurantium (6 g), Pinellia ternata (6 g) ad Caulis bambusae (6 g) | Glycyrrhiza radix; Liquorice root; Pericarpium of mandarin orange (dried and ripe peel); Bitter orange, Citrus reticulata, Blanco | Panax ginseng C. A. Meyer | Fabaceae | G. uralensis |
| 17   | Leong et al. (2013) | Herbal formula MCC: Mamordica charantia, the pericarp of Citri reticulate and L-carnitine | Bittermelon; | Pinellia ternata, (Thunb.) Makino | Phytolacca nigravaria. (Mitford) Rendie | Rutaceae | C. reticulata |
| 18   | Tan et al. (2011) | Chinese herbal extract (SK0506): Gynostemma pentaphyllum, Coptis chinensis and Salvia miltiorrhiza (gypenosides, berberine and tanshinone) | Jiaogulan Huang Lian | Red sage, Chinese ginseng | Gynostemma pentaphyllum (Thunb.) Makino | Ranunculaceae | G. pentaphyllum |
| 19   | Liu and Shi (2015) | Yi Tang Kang sugar, Poria cocos, atractylodes, Radix chiray, red ginseng and other drugs | Baizhu | obtained from roots of sunflower family; Red ginseng (produced by steaming and drying fresh and raw ginseng), Botrypus thetis Wall | Astereaceae/Compositae | A. macrocephala |
| 20   | Lim et al. (2019) | SCH Pharbitis semen; Trogopterorum Faeces, Cyper Rhizoma = 2:1:1 | Atractylodes macrocephala Koidz. | Panax ginseng C.A. Meyer | Convolvulaceae | T. xanthipes |

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| S.No | Reference | Name of the Combination | Components | Chinese Name | Common name | Scientific name | Family | Specie |
|------|-----------|-------------------------|------------|--------------|-------------|----------------|--------|--------|
| 21   | Ahmed et al. (2009) | Marjoram and chicory | Marjoram dry leaves (Origanum majorana) and chicory dry leaves (Cichorium intybus) (1:5 w/v in water) | Marjoram dry leaves | Trogopterus xanthipes, (Migne-Edwards) | Lamiaceae | C. majorana |
|      |           |                         |             | chicory dry leaves; Common chicory | Gynerus rotundus L. | Asteraceae | C. intybus |
| 22   | Jang et al. (2018)  | Gambihwan (GBH1)       | Ephedrae Herba; Coicis semen; Menthae herba Gypsum; Alismatis Rhizoma; Crataegi fructus; Arecae semen; Hordei fructus germinatus. | Ephedrae Herba | Origanum majorana L | Ephedraceae | E. sinica |
|      |           |                         |           | Job's tears seed or adlay; Coix seed; Coicis semen; Menthae herba Alisma; Asian water-plantain; mad-dog weed | Cichorium intybus L | Poaceae/ Gramineae | C. lacryma-jobi |
|      |           |                         |           | GBH2: Ephedrae herba; Coicis semen; Typhae pollen; Castanaeae semen; Sinomeni Caulis et Rhizoma; Scutellariae radix | | | |
|      |           |                         |           | Bo He | Ephedra sinica Stapf | Lamiaceae | M. Haplocalycis |
|      |           |                         |           | | Coix lacryma-jobi L. | Alismataceae | A. orientale |
|      |           |                         |           |               | Arecae semen; areca; bets nut, areca nut | Rosaceae | C. monogyna |
|      |           |                         |           | Malt Barley Sprout; germinated barley; (Hordei fructus germinates) | Crataegus monogynaJacq | Poaceae/ Gramineae | H. vulgare |
|      |           |                         |           | Sheng Pu Huang | Typha Pollen, Cattail Pollen, Bulrush Castanaeae semenDried Chestnut | Typhaceae | T. angustifolia |
|      |           |                         |           | | Hordeum vulgare L | Sapindaceae | A. hippocastanum |
|      |           |                         |           | Boi | Sinomeni Caulis et Rhizoma | Menispermaceae | S. acutum |
|      |           |                         |           | Baikal | Skulcap or Chinese skullcap (Radix scutellariae) | Aesculus hippocastanum L | Lamiaceae | S. baicalensis |
| 23   | Wat et al. (2018)   | combination of sylmarin, Schisandrae Fructus, Crataegus Fructus and Momordica charantia (1:1:1:1) | Sylmarin (flavanolignans extracted from the milk thistle Silybum marianum (L.)) | | Snomenium acutum (Thunb.) Rehder and E.H.Wilson | Asteraeaceae | S. marianum |
|      |           |                         |           | Magnolia-Vine, Chinese magnolia-vine, schisandra (Schisandrae Fructus) | Scutellaria baicalensis, Georgi | Schisandraceae | S. chinensis |
|      |           |                         |           | | | |
| 24   | Park et al. (2009) | Herbal Complex (HC) extract | Dioscorea Rhizoma, Glycine soja Steb. et Zucc, Bombycs corpus, Fermented Glycine soja | SanYak | Crataegus monogyna Jacq | Dioscoreaceae | D. polystachya |
|      |           |                         |           | | Momordica charantia L. | Leguminosae/ Fabaceae | G. soja |

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hypertriglyceridemia, low HDL, high blood sugar (>100–125 mg/dl).

3. Adults >17 years < 74 years.

Exclusion Criteria
1. Review article.
2. Effect of individual herbs on MetS
3. Effect of interventions through diet, low caloric, mediterranean diet etc., on MetS.
4. Any MetS model used but not for the purpose of assessing effect on MetS, rather individual aspect such as obesity, non-alcoholic fatty liver disease and non-alcoholic steatohepatitis and polycystic ovary syndrome.

Data Analysis and Study Design
All the polyherbal formulations were classified taxonomically and then effect of intervention and evaluation of results were done, based on number of MetS criteria met both in animal and/or humans.

Quality of animal-based studies were assessed by using a qualitative scoring system using 8 questions. Maximum score achieved was 8, with yes = score 1 and no = score 0 with following questions:

1. MetS parameters assessed >3 = score 1; ≤3 = score 0
2. MetS parameters met: 3 out of 5 parameters (good Effect) = 1; <3 out of 5 (not so good) = 0
3. Dosage of herb provided: Yes = 1; No = 0
4. Components and rationale for dosing: yes = 1; no = 0
5. Animal ethical approval: Yes = 1; No = 0
6. Euthanasia protocol mentioned/followed: Yes = 1; No = 0
7. Model validated for MetS: Yes = 1; No = 0
8. Positive control used: Yes = 1; No = 0

For clinical trial we adopted a mixed model for assessing our articles including SPICE (S = setting; P = population; I = intervention/what; C = comparison/controls E = evaluation/with what result) (Booth, 2006; Cleyle and Booth, 2006) and SPIDER (S = Sample P = phenomenon of interest/intervention I = intervention size, D = design, E = evaluation/outcome R = research type; qualitative, quantitative or mixed type). SPIDER methods had added points for assessing both qualitative and quantitative methods (Cooke et al., 2012). Further aspects of quality of clinical trial were assessed based on following aspects with yes = 1; No = 0 according to an adopted guideline for critical appraisal (Alcántara et al., 2011):

1. The study addresses an appropriate and clearly focused question
2. The assignment of subjects to treatment groups is randomized.
3. An adequate concealment method is used
4. The design keeps subjects and investigators ‘blind’ about treatment allocation.
5. The treatment and control groups are similar at the start of the trial.
6. The only difference between groups is the treatment under investigation.
7. All relevant outcomes are measured in a standard, valid and reliable way
8. What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?
9. All the subjects are analyzed in the groups to which they were randomly allocated (often referred to as intention to treat analysis)
10. Where the study is carried out at more than one site, results are comparable for all sites.

Besides, following questions were also assessed: concentration of the herb provided or not, quality control

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TABLE 1 | (Continued) Taxonomic classification of all the polyherbal combinations reviewed in animal Studies.

| S.No | Reference | Name of the Combination | Components | Chinese Name | Common name | Scientific name | Family | Specie |
|------|-----------|-------------------------|------------|--------------|-------------|----------------|--------|--------|
| 1.   |           | Bomyx corpus a drug consisting of the dried larva of silkworm, dead and stiffened due to the infection of fungus Beauveria bassiana (Bals.) Vuill. | Dioscorea polystachya, Turciz. | Glycine max subsp. soja (Siebold and Zucc) | Leguminosae/Fabaceae | G. soja |
| 2.   |           | fermented Glycine soja; cultivated soybean | Cordyceps B. bassiana | Bombyx Batryticatus (silkworm infected of fungus Beauveria bassiana (Bals.) Vuill.) | Glycine max [L.] Merr | B. bassiana |
| S. No | References | Name of the herb | Components | Chinese Name | Common name/source | Scientific name | Family | Specie |
|-------|-------------|------------------|------------|--------------|---------------------|----------------|--------|--------|
| 1     | Tian-zhan et al. (2019) | Yiqi Huazhuo Guishen herbal formula | Huang qi (Astragalus membranaceus); Huanglian (Coptis chinensis); Shengpuhuang (Pollen typhae); Ze Xie (the rhizome of oriental water plantain); Lu Dou Yi (Mung bean peel); Liu Yue Xue (Serissa serissoides); Zhi-fuzi (Radix Aconiti lateralis praeparata) | Huang Qi | Mongolian milkvetch; root of Astragalus Radix astragali | Astragalus membranaceus (Flisch.) Bunge: Astragalus propinquus Schischkin | Fabaceae | A. membranaceae |
|       |             |                  |            | Huang Qian | Chinese goldthread or canker root | Coptis chinensis Franch; Coptis deltoidea C.Y. Cheng et Hsiao, and Coptis teeta Wall | Ranunculaceae | C. chinensis; C. deltoidea and C. teeta |
|       |             |                  |            | Sheng Pu Huang | Typha Pollen | Typha angustifolia L. | Typhaceae | T. Angustifolia |
| 2     | Wang et al. (2013) | Yiqi Huaju Qingli | Huangqi (Radix Astragali); Huanglian (Rhizoma Coptidis); Pu huang (Pollen Typhae); Ze Xie (Artemisiae Rhizoma Alismatis); Lu Dou Yi (Testa Vignae Radiatae); Liu Yue Xue (Serissa Japonica); Fuzi (Radix Aconiti Lateralis Praeparata) | Details similar as previous except slight difference in methods of collection of the extracts | | | | |
| 3     | Farajbakhsh et al. (2019) | Sesame oil and vitamin E | Curcuma longa and Nigella sativa | Diabegon | Sesame oil Vitamin E | Sesamum indicum L. a-tocopherol | Pedaliaceae | S. indicum |
| 4     | Amin et al. (2015b) | Curcuma longa and Nigella sativa | Morinda charantia, Gymnema sylvestre, Trigonella foenum-graecum, Plumbago zeylanica, Eugenia jambolana, Aegle marmelos, Terminalia chebula, Terminalia balecica, Emblica officinalis, Cucumis longa, Pterocarpus mampipum, Barbarea aristata, Cyrtophyllum rubifolius, Cyperus rotundus, Piper longum, root of Piper longum, Zingiber officinale, and Asphalatium punjabinum | Chirata; Chireta | Swertia chirayita (Roxb.) Buch.-Ham. ex C.B.Clarke Gymnema sylvestre (Retz.) Schult | Swertia chirayita (Roxb.) Buch.-Ham. ex C.B.Clarke Gymnema sylvestre (Retz.) Schult | Gentianaceae | S. chirayta |
| 5     | Yadav et al. (2014) | Morinda charantia, Gymnema sylvestre, Trigonella foenum-graecum, Plumbago zeylanica, Eugenia jambolana, Aegle marmelos, Terminalia chebula, Terminalia balecica, Emblica officinalis, Cucumis longa, Pterocarpus mampipum, Barbarea aristata, Cyrtophyllum rubifolius, Cyperus rotundus, Piper longum, root of Piper longum, Zingiber officinale, and Asphalatium punjabinum | Bittermelon; Balsam Pear | Fenuagreek | Trigonella foenum-graecum L. Plumbago zeylanica L. | Trigonella foenum-graecum L. Plumbago zeylanica L. | Fabaceae/ Leguminosae | T. foenum-graecum P. zeylanica |
|       |             |                  |            | Plumbago; Ceyton leadwort; doctorbush or wild leadvort | | | | |
|       |             |                  |            | Jamon; Java Plum | | | | |
|       |             |                  |            | Bael, Bengal Quince | | | | |
|       |             |                  |            | Chebulic myrobalan, harial; black- or chebulic myrobalan | | | | |
|       |             |                  |            | Emblica myrobalan | | | | |

(Continued on following page)
| S. No | References | Name of the herb                                                                 | Components                                                                 | Common name/source | Scientific name | Family | Specie |
|-------|------------|----------------------------------------------------------------------------------|----------------------------------------------------------------------------|--------------------|-----------------|--------|--------|
|       | Yang et al. (2014b) | Modified Lingyzhugan decoction (MLD)+ weekend fasting | Dangshen (Radix Codonopsis) 20 g, GuZhi (Ramulus Cinnamomi) 12 g, Fuling (Poria) 30 g, Baihu (Rhizoma Atractyloides Macropaphala) 15 g, Gancao (Radix Glycyrrhizae) 6 g, Dahuang (Radix et Rhizoma Rhei Palmat) 9 g | Dangshen | Radix Codonopsis pilosula (mixture) | Codonopsis pilosula (Franch.) Nanrif | Campanulaceae | C. pilosula, C. pilosula var. modesta and C. tangshen |
|       | Yu et al. (2018) | Dahuang Huanglian Xiebin Decotion (JTTZ) | Aloe vera, Copotis chinensis, Rhizoma Anemarrhenae, red yeast rice, Momordica charantia, Salvia miltiorrhiza, Schisandra chinensis, and dried ginger | Luhui Huanglian Zhi mu | Aloe vera | Aloe vera, (L.) Burm.f | Asphodelaceae | A. vera |
|       |             |                                                                                   |                                                                            | Hong qu            | Chinese goldthread | Coptis chinensis, Franch | Ranunculaceae | A. chinensis |
|       |             |                                                                                   |                                                                            |                    | Rhizoma Anemarrhen | Anemarrhena asphodeloides, Bunge | Asparagaceae | A. asphodeloides |
|       |             |                                                                                   |                                                                            |                    | red yeast rice (purple fermented rice, cultivated with the mold Monascus purpureus) | Monascus purpureus, (Went, 1895) | Monascaceae | M. purpureus |
|       |             |                                                                                   |                                                                            |                    |                 |                     |               |        |
|       |             |                                                                                   |                                                                            | Kugua              | Bittermelon; Balsam Pear | Momordica charantia L | Cucurbitaceae | M. charantia |
|       |             |                                                                                   |                                                                            | Danshen Wuweizi    | Red sage, Chinese sage Magnolia-vine, Chinese magnolia-vine, schisandra | Salvia miltiorrhiza, Bunge Schisandra chinensis (Turcz.) Ball | Lamiaceae | S. miltiorrhiza |
|       |             |                                                                                   |                                                                            | Ganjiang           | Dried ginger | Zingiber officinale Roscoe | Zingiberaceae | Z. officinale |

(Continued on following page)
| S. No | References | Name of the herb | Components | Chinese Name | Scientific name | Family | Specie |
|-------|------------|-----------------|------------|--------------|----------------|--------|--------|
| 8     | Rozza et al. (2009) | Armolipid Prev, Rottapharm, Monza, Italy | Combination of Ortosiphon staminensis, with policosanol (dietary supplement), red yeast rice extract, berberine, folic acid and coenzyme Q10 | Miliai, kucing and kunri kucing policosanol (mixture of alcohols isolated from Cuban sugar cane wax, Red yeast rice extract (purple fermented rice, cultivated with the mold Monascus purpureus), Berberine (chemical in Berberis genus), Folic acid (obtained from food source), coenzyme Q10 | Orthosiphon staminensis Berth Lamiaceae O. stamineus | Poaceae | S. officinarum |
| 9     | Castellino et al. (2019) | Cynara cardunculus (L.) subsp. scolymus Hayek-based nutraceutical, named Altilix | Cynara cardunculus (L.) subsp. scolymus Hayek; Chlorogenic Acid and Luteolin | Artichoke; cardoon | Chlorogenic Acid (ester of caffeic acid and-quinic acid) Luteolin | Cynara cardunculus (L.) Asteraceae | Coenzyme C16H18O9 | Dietary polyphenol |
| 10    | Panahi et al. (2015) | Curcuminoids (Curcumin C3 Complex®, Sami Labs LTD, Bangalore, India; piperine (Bioperine®; Sami Labs LTD, Bangalore, India) was added to enhance Bioavailability) | 95% curcuminoids (70% is curcumin; remaining demethoxycurcumin and bisdemethoxycurcumin in patented ratio. Curcuminoids obtained from turmeric 5% piperine (obtained from black pepper) | Curcuma longa L Zingiberaceae | Curcuminoids (curcumin; demethoxycurcumin and bisdemethoxycurcumin) Piperine | Piper nigrum L Piperaceae | C. longa |
| 11    | Panahi et al. (2014) | Curcuminoids (piperine was added to enhance Bioavailability) | 95% curcuminoids (70% is curcumin; remaining demethoxycurcumin and bisdemethoxycurcumin in patented ratio. Curcuminoids obtained from turmeric 5% piperine (obtained from black pepper) | Curcuma longa L Zingiberaceae | Curcuminoids (curcumin; demethoxycurcumin and bisdemethoxycurcumin) Piperine | Piper nigrum L Piperaceae | P. nigrum |
| 12    | Verhoeven et al. (2015) | Red yeast rice (obtained by culturing the yeast Monascus purpureus on rice) and olive extract | Red yeast rice (obtained by culturing the yeast Monascus purpureus on rice) and olive extract | Red yeast rice (Purple fermented rice, cultivated with the mold Monascus purpureus) olive extract | Monascus purpureus, (Went, 1895) Oleaceae | Olea europaea L Oleaceae | O. europaea |
| 13    | He et al. (2007) | Yiqi Sanju Formula | Details not available as paper is in Chinese | Red yeast rice | Monascus purpureus, (Went, 1895) Monascaceae | Monascaceae | M. purpureus |
| 14    | Lee et al. (2012) | Red yeast rice, bitter gourd, chlorella, soy protein, and licorice | Red yeast rice, bitter gourd, chlorella, soy protein, and licorice | Red yeast rice | Monascus purpureus, (Went, 1895) Monascaceae | Monascaceae | M. purpureus |
of the combination assessed or not and chemical classification done or not.

RESULTS

The selection parameter, applied filters, as well as output of all the searches, are summarised in Figure 1A. In Figure 1B the summary of identified results is presented according to PRISMA guidelines (Page et al., 2019; Maraolo, 2021).

The total reference shortlisted were 109, out of which duplications and or articles which could not be retrieved were removed (n = 15) and number of articles to review were 94. Out of total 94 articles, 26 were divided as clinical trials and remaining 68 articles were either based on animal studies or in-vitro assays. These articles were further shortlisted by reviewing their basic theme and it was identified that some of the articles did not have the objective to manage MetS or were aimed at identifying new targets for management of MetS such as use of probiotics or correlating with gut microbiota (Ni et al., 2018) or the basic target for those studies were to cater different disease, although parameters for MetS were being met. Hence, out of 68 animal studies, filtered animal studies were identified to be 24 which matched our main objective of MetS. The taxonomic classification of polyherbal combinations used both in animal and clinical studies are summarized in Tables 1, 2, respectively. The meta-analysis of animal studies is summarized in Table 3. To further analyze the quality of studies, a semiquantitative scale was used, the details of which are presented separately as Table 4. The maximum score was 8, and references have been aligned from highest score to lowest score.

Out of 26 clinical trial articles, 15 articles matched our main objective, and their meta-analysis is presented in Table 5 according to SPIDER model with references. Supplementary Table S1 is attached to shows the analysis by SPICE protocol along with information about other targets met besides the 5 parameters of MetS. Table 6 summarizes the qualitative scoring based on a checklist as mentioned in analysis section along with the online link available for the same. Out of 15 polyherbal combinations that were reviewed three formulations were able to modify 4 MetS parameters clinically. They include Yiqi Huazhuo Gushen herbal formula (Tian-zhan et al., 2019), Yiqi Huaju Qingli Formula (Wang et al., 2013), Sesame oil and vitamin E (Farajbaksh et al., 2019). Six polyherbal combinations were able to reduce three out of 5 standard MetS parameters. The combinations included, Carcuma longa and Nigella sativa (Amin et al., 2015b), Diabegon (Yadav et al., 2014), modified Linguizhugan decoction (MLD)+ weekend fasting (Yang et al., 2014a), Dahuang Huanglian Xiexin Decoction (Yu et al., 2018), combination of Nutraceuticals (Rozza et al., 2009) and Altlix supplement containing chlorogenic acid and luteolin (Castellino et al., 2019).

DISCUSSION

MetS is a cluster of metabolic abnormalities that appear as a pre-diseased state and predisposes to CVD risk even before overt disease such as diabetes or hypertension develops. Catering those risk factors at this stage could prevent incidence of CVD. Hence, clinicians need to target multiple risk factors simultaneously. As the incidence of MetS is rising, there is a need to identify therapeutic modalities that could address multiple disease targets, offer better compliance, and reduce risk of adverse effects (Reilly and Rader, 2003; Keith et al., 2005). Polyherbal formulations could mutually enhance pharmacological synergy on the targeted disease and often exhibit pharmacological and therapeutic superiority in comparison to isolated single constituents.

The current review focuses on studies published from 2005–2020, reporting the efficacy of polyherbal therapies in MetS. This is attributed to either the action of bioactive ingredients from different herbs on the same molecular target forming a multiple-drug-one-target model (additive effect) and/or the functionally diverse targets but with potentially clinically relevant associations forming a multiple-drug-multiple-target-one-disease (synergistic effect) (Lu et al., 2012; Wang et al., 2012). In the current review, we identified 25 animal based studies in which polyherbal formulations were used in animal models of MetS. We categorised them as good and not very good, based on the

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### TABLE 2 | (Continued) Taxonomic classification of all the polyherbal combinations used in clinical studies against metabolic syndrome.

| S. No | References | Name of the herb Components | Chinese Name | Common name/source | Scientific name | Family | Specie |
|-------|------------|----------------------------|--------------|---------------------|----------------|--------|--------|
| 15    | Nagata et al. (2012) | Keishibukuryogan (Guizhi-Fuling-Wan) | Cinnamomi Cortex, Paeoniae Radix, Moutan Cortex, Persicae Semen, and Hoelen | Guizhi | Cinnamoni cortex (dried bark of Cinnamomum verum); Chinese cinnamon | Cinnamomum verum J.Presi | Lauraceae | C. verum |

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TABLE 2 | (Continued) Taxonomic classification of all the polyherbal combinations used in clinical studies against metabolic syndrome.
| S. No | Polyherbal combination | Model/animal/treatment duration | Parameters assessed: 5 = glucose/FBG, TG, HDL-C, BP and central obesity (weight, BMI and HC). Parameters met: BMI [WC, HC], BP, HDL, TG, FBG. Additional: TC, LDL | Other parameters related to MetS | Score of study MetS parameters assessed >3 = 1; ≤3 = 0 | Score for effects (3/5: Good) = score 1; <3/5 (not so good) = score 0 | Concentration given | Quality control | Chemical classification | References |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Curcuma longa, Salacia reticulate, Gymnema sylvestre, Emilia offinialis, Terminalia chebula | High fructose diet/ Wistar rats/3 weeks | Assessed: 5/5 = Body weight, abdominal waist, BP, glucose, TG, HDL-C, TC, LDL and VLDL. Met: 5/5 = Lowered Body weight, abdominal waist and BMI, reduced BP, AI, improved FBG and OGTT, reduced TG, increased HDL-C. Also, TC, LDL and VLDL reduced | Reduced SGOT, SGPT, Uric acid, MDA. Reduced gastrocnemius muscle weight and fat pads. Reduced infiltration of inflammatory cells and fat accumulation in liver and pancreas | 1 | 1 | Yes | No | No | Thota et al. (2014) |
| 2 | DHSGT: Glycyrrhiza uralensis Fischer (40 g), Rheum undulatum Linne (80 g), Prunus persica Linne (60 g), Cinnamomum cassia Presl (40 g), and Natrii Sulfas (40 g) | HFD-induced obesity/ C57BL/6 J mice/ 7 weeks | Assessed: 5/5 = Body weight, BP, TG, HDL, Glucose. TC and LDL, Met: 5/5 = Reduced body weight (Reduced liver weight and adipose tissue mass, adipocyte size), BP, TG, glucose and increased HDL-c. TC and LDL-c reduced | Decreased serum leptin and leptin mRNA expression. Increased mRNA expression of peroxisome proliferator activated receptor-gamma, uncoupling protein-2, and adiponectin in visceral adipose tissue of HFD mice. Inhibition of porcine pancreatic lipase and ACE activities in vitro | 1 | 1 | Yes | No | No | Sung et al. (2014) |
| 3 | Huang-lian-je-du-tang: Rhizoma coptidis, Radix scutellariae, Cortex phellodendri and Fructus gardeniae (3:2:2:3) | Obese-diet (2% fat, 10% sucrose, 6% salt and 8% defatted milk powder) and drinking water (20% sucrose solution) ad libitum/ Wistar male rats/ 12 weeks | Assessed: 5/5 = BP, body weight, FBG, fasting insulin, and insulin resistance index, TG, HDL-C. LDL-c. Met: 5/5 = Reduction in body weight, BP, FBG, fasting insulin and insulin resistance index, TG levels reduced, and HDL-c increased. LDL-c reduced | Reduced leptin, CRP and glutamic-oxaloacetic transaminase, Decreased VCAM-1, ICAM-1, E selectin, MCP-1 and improved PPAR-y expression. Lipid droplets in liver decreased | 1 | 1 | Yes | Yes | No | Li et al. (2013) |
| 4 | RGPM: Red ginseng and Polygonum Multiflor/ Radix (1:1) | High fructose/SD rats/ 6 weeks | Assessed: 5/5 = body weight, Glucose, BP, TG, HDL-c. TC and LDL-c. Met: 5/5 = Reduced body weight and epididymal fat pads weight, reduced TG, systolic BP and increased HDL-c, OGTT improved. TC and LDL-c reduced | reduced lepin, CRP and glutamic-oxaloacetic transaminase, Decreased VCAM-1, ICAM-1, E selectin, MCP-1 and improved PPAR-y expression, lipid droplets in liver decreased | 1 | 1 | Yes | No | No | Kho et al. (2016) |
| 5 | Modified Ingguizhugan decoction with dietary restriction and exercise. [Poria cocos Wolf, Cinnamomum cassia Presl, Atractylodes lancea DC., Glycyrrhiza uralensis Fischer., Cinnamomum cassia Presl, Atractylodes lancea DC., Cinnamomum cassia Presl., Atractylodes lancea DC., Cinnamomum cassia Presl., Atractylodes lancea DC., Cinnamomum cassia Presl., Atractylodes lancea DC., Cinnamomum cassia Presl., Atractylodes lancea DC.] (ratio of 12:9:6:6:9:9) | HFD for 12 weeks (30% HFD + dietary restriction ± 45 min swim/adult SD male rats/1 week after HFD for subsequent 12 weeks | Assessed: 5/5 = body weight, HC, TG, HDL, BP, blood glucose. Met: 5/5 = reduced body weight, TG, BP, blood glucose and insulin levels, Increased HDL. Reduced TC, LDL, adipose and liver tissue weight | Reduced serum FFA, AST, ALT and ALP and TNF-a, leptin in serum and liver | 1 | 1 | Yes | Yes | Yes | Yao et al. (2017b) |

(Continued on following page)
| S. No | Polyherbal combination | Model/animal/treatment duration | Parameters assessed: 5 = glucose/FBG, TG, HDL-C, BP and central obesity (weight, BMI, HC and WC). Parameters met: BMI (WC, HC), BP, HDL, TG, FBG. Additional: TC, LDL | Other parameters related to MetS | Score of study MetS parameters assessed | Score for effects (3/5: Good = score 1; <3/5 (not so good) = score 0) | Concentration given | Quality control | Chemical classification | References |
|-------|------------------------|---------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------|---------------------------------|---------------------------------|--------------------------|--------------------------|---------------------------|---------------------|
| 6     | Curcuma longa and *Alilea sativa* | Fructose fed rats (60% fructose in diet + white flour instead of wheat flour) for 6 weeks/SD rats/8 weeks | Assessed: 5/5 = body weight, BP, Fasting serum insulin, FBG, HDL, and TG; Met: 4/5 = Reduced BP, TG, FBG, increased HDL. Reduced LDL, TC and insulin | CRP reduced | 1 1 | Yes | No | Yes | No | Amin et al. (2015a) |
| 7     | Soybean meal and probiotics (Bifidobacterium, longum (BB536)) | Obese Zucker rats/Rat/100 days (14.2 weeks) | Assessed: 4/5 = Body weight, TC, TG, HDL and glucose. Met: 4/5 = Reduced weight gain (reduced liver weight and fat), FBG and insulin, TG and increased HDL. Reduced TC and LDL. | Reduced food intake, ALT, GGT, ALP | 1 1 | Yes | No but the diet was purchased commercially | No | Mounts et al. (2015) |
| 8     | ACE: *Artemisia iwayomogi* and Curcuma longa (1:1) | HFD (10 weeks)/C57BL/6 male mice/10 weeks | Assessed: 4/5 = Body weight, TG, FBG, HDL-c (TC and LDL-c). Met: 4/5 = Reduced body weight (reduced liver weight, epididymal, retroperitoneal, and visceral adipose tissues. Reduced adipocyte size, TC and TG in liver), reduced serum TG, FBG and increased HDL. Reduced LDL-c and TC. | PPAR-γ, fatty acid synthase; SREBP-1c; and PPAR-α | 1 1 | Yes | Yes | Yes | Lee et al. (2015b) |
| 9     | Fu Fang Zhen Zhu Tiao Zhi formula (FTZ): Ligustrum lucidum W.T. Alton, fructus; Atractyloides macrocephalae Koidz., rhizoma; Salvia miltiorrhiza Bunge, radix; Coptis chinensis Franch., rhizoma; Panax notoginseng F.H.Chen, radix; Eucommia ulmoides Oliv., cortex; Crinum japonicurn Fisch. ex DC., radix; Citrus medica var sarcodactylus Swingle, fructus | HFD and insulin resistant HepG2 cell lines/Male SD rats/8 weeks | Assessed: 4/5 = Body weight, FBG, TG, HDL-c. TC. Parameters met: 4/5 = Reduced body weight, FBG (HOMA-IR index), TG increased HDL-c. reduced TC. | Increased PI3K p85 mRNA expression in the adipose tissues. Reduced glucose content, PI3K p85 mRNA and IRS1 protein expression upregulated in insulin resistant HepG2 cells | 1 1 | Yes | Yes | Yes | Hu et al. (2014) |
| 10    | Erchen decoction: Pericarpium Citri Reticulatae (9 g), Rhizoma Pinelliae (9 g), Poria (6 g) and Radix Glycyrrhizae (3 g) | HFD for 10 weeks/Male C57BL/6J mice/4 weeks | Assessed: 4/5 = glucose, TG, HDL, obesity, Met: 3/5 = reduced Body weight, Abdominal circumference, FBG and improved GGT, no effect on insulin levels. Reduced TG but no effect on HDL-c and LDL-c. Reduced TC. | Increased CDKAL1 expression in the liver, visceral and subcutaneous adipose tissues increased, improved islet cell function to secrete more insulin | 1 0 | Yes | No | No | Gao et al. (2015) |

(Continued on following page)
| S. No | Polyherbal combination                                                                 | Model/animal/treatment duration                                                                 | Parameters assessed: 5 = glucose/FBG, TG, HDL-C, BP and central obesity (weight, BMI, HC and WC). Parameters met: BMI (WC, HC), BP, HDL, TG, FBG. Additional: TC, LDL | Other parameters related to MetS | Score of study MetS parameters assessed >3 = 1; <3 = 0 | Score for effects (3/5: Good = score 1; <3/5 (not so good) = score 0 | Concentration given | Quality control | Chemical classification | References |
|-------|---------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------|-------------------------------|-----------------------------------------------------|-----------------------------------------------------|-----------------|-----------------|-------------------|-----------|
| 11    | CPQ: Curcumin, Piperine and Quercetin in a ratio 94:1:5                                | HFD and Low-Dose Streptozotocin (8 weeks)/Albino female Wistar rats/28 days                    | Assessed: 4/5 = body weight, Glucose, TG, HDL (LDL and TC also assessed), Met: 3/5, improved glucose tolerance, reduced TG and increased LDL-LDL-c and TC reduced | Increased catalase, glutathione, and SOD. Decreased granular degeneration in diabetic liver | 1                                                  | 1                                                  | yes             | yes             | Yes                | Gao et al. (2015) |
| 12    | Extracts of Salvia miltiorrhiza + Gardenia jasminoides                                 | HFD/SD male rats/4 weeks                                                                         | Assessed: 4/5 = Body weight, Serum glucose levels, TG, HDL-c (TC, and LDL-C). Met: 3/5 = Reduced serum TC, TG, body weight (reduced visceral fat mass), glucose, enhanced insulin sensitivity. TC and LDL-c reduced | Reduced Serum non-esterified fatty acids, ALT and AST, adipokines, TNF-α and IL-6. Increased leptin in adipose tissue. Enhanced leptin expression | 1                                                  | 0                                                  | Yes             | Yes             | Yes                | Tan et al. (2013) |
| 13    | SUB885C: Fructus Orolae, Folium Nelumbinis, Folium Apocyni, Flos Rosa rugosae, Radix et Phizoma Rhei, Depuratum minabilium, Thalusi Sargassi, and honey fried Radix Glycyrrhizae | ApoE3Leiden.CETP transgenic mice with mild hypercholesterolemia on semi-synthetic modified Western-type diet (0.2% cholesterol, 15% saturated fat and 40% sucrose; Cell line: 3T3-L1 preadipocyte/Mice/4 weeks | Assessed: 3/5 = Body Weight, TG, HDL-c. also TC, Met: 2/5 = Reduced TG, increased LDL-C. Also reduced TC | Reduced CETP, vLDL-c and TGs. Stimulated lipolysis and inhibited adipogenesis in 3T3-L1 cells | 0                                                  | 0                                                  | Yes             | Yes             | No                 | Wei et al. (2012) |
| 14    | Bofu-tsu-shosan formula: Glycyrrhiza radix, Schizonepetae spica, Ephedrae herba, Forsythiae fructus Others: Platycodi radix, Gypsum Fibrosum Atractyloids rhizoma, Rhei rhizoma, Scutellariae radix, Gardeniae fructus, pinonai radix, cimdi rhizoma, Angelicae radix, Menthae herba, Ledebouriellae radix, Zingiberis rhizoma, Kadsurni, Natrium sulfuricum | KKAy mice 9 weeks of age/mice/8 weeks 4.7% BOF (Chronic model), 14 weeks KKAy mice/male mice/5,000 mg/kg BOF dissolved in 1ml of distilled water per 100 g of body weight for 1 day (Acute model) | Assessed: 4/5 = obesity with marked visceral fat, blood glucose, HDL, and BP. Met: 2/5 = Lowered Body weight, obesity, BP. LDL reduced. No effect on non-FBG, TC, HDL. | Food intake reduced; White adipose tissue (weight and cell size decreased); expression of genes increased: adiponectin and PPAR receptors; reduction in plasma acylated-ghrelin genes expression (antihypertensive effect) | 1                                                  | 0                                                  | Yes             | No, but ingredients were recruited from commercial manufacturers | No                | Azushima et al. (2013) |
TABLE 3  (Continued) Summary of metaanalysis of Poly herbal combinations used in animal-based models of Metabolic syndrome.

| S. No | Polyherbal combination | Model/animal/treatment duration | Parameters assessed: 5 = glucose/FBG, TG, HDL-C, BP and central obesity (weight, BMI and WC). Parameters met: BMI [WC, HC], BP, HDL, TG, FBG. Additional: TC, LDL | Other parameters related to MetS | Score of study MetS parameters assessed >3 = 1; <3 = 0 | Score for effects (3/5: Good) = score 1; <3/5 (not so good) = score 0 | Concentration given | Quality control | Chemical classification | References |
|-------|------------------------|---------------------------------|-----------------------------------------------------------------------------------------------------------------|-------------------------------------|-------------------------------------------------------|-----------------------------------------------------------------|-----------------|---------------------|------------------|------------------|-------------------|
| 15    | Tang-Nai-Kang: Fructus Ligustri Lucidi, Spica Prunellae vulgaris, Saururus chinensis, Podium guajava and Radix ginseng (25:10:15:10) SHR, Cg-Lepr/NDo1cr (SHR/cp) for disease and WKY rats for control/male rat 7 weeks/low and high dose 2 weeks | Assessed: 4/5 = BP, sugar, SBP, bodyweight and fat, TG, Met. 4/5 = reduced SBP, body weight and fat mass, FBG, insulin levels. Insulin resistance (OGTT and ITT) was reduced. TC levels did not reduce significantly | AST, ALT, FFA reduced. Gene expression of NAD+-dependent deacetylase E10 and genes related to fatty acid oxidation were markedly up-regulated in the muscle, liver and adipose tissues | 1 | 1 | Yes | No but the process was carried out by Sichuan Medco Pharmaceutical Limited Corporation (Deyang, China), hence some validation is expected | Yes | Li et al. (2015) |
| 16    | Wendan decoction: Radix Glycyrrhizae (3g), Perniciparum Citri Reticulatae (9g), Poria Cocos (4.5g), Citrus Aurantium (6g), Pinellia ternata (6g) and Caulis Bambusae (8g) High-sugar-fat-diet (15 weeks) and high-fat emulsion (2 weeks)/Wistar male rat/2 weeks | Assessed: 3/5 = abdominal perimeters, serum insulin HOMA-IR, HDL. Met: 3/5 = decrease in abdominal perimeters and serum insulin levels, increases in HLDL levels, Recovered the HOMA-IR to the control level | pathway analysis and molecular docking simulation | 0 | 1 | Yes | Yes | Yes | Chen et al. (2017) |
| 17    | MCC: Monorchidca charantia, the pericarpium of Citri reticulata and L-carnitine Dosage: 6 g/kg | Assessed: 4/5 = weight gain, FPG and glucose intolerance, insulin sensitivity, TG, HDL (LDL also assessed). Met: 2/5 = reduced TG, FPG, glucose intolerance and Insulin sensitivity index, LDL/HDL ratio and TC levels also reduced | Mitochondrial coupling efficiency of skeletal muscle was improved and reduced carnitine palmitoyl CoA transferase activity | 1 | 0 | Yes | No, but commercial preparation was manufactured and supplied by Infinitus (China) Company Ltd., Guangzhou, China | No | Leong et al. (2013) |
| 18    | Shi-Moto: Glycyrrhiza pentaphyllum, Coptis chinensis and Salvia miltiorrhiza (gypenosides, berberine and tanshinone) HFD/Male SD rats/4 weeks | Assessed: 3/5 = Body weight, FBG, TG, TC. Parameters met: 3/5 = Lowered body weight, visceral fats, TG, slightly reduced FBG. (Reduced insulin level and NAFA, improved impaired glucose tolerance and glucose infusion rate). TC reduced | Enhanced GLUT4 expression in adipose tissue, enhanced insulin mediated glucose uptake in red quadriceps and white gastrocnemius skeletal muscles, enhanced glycogen synthesis | 0 | 1 | No (but yield is given. It seems all powders were taken in equal ratio) | Yes | Tan et al. (2011) |
| 19    | Yi Tang Kang: sugar, poria cocos, Atractylodes, radix Astragalae, red ginseng and other drugs MS spleen deficiency syndrome rats with HFD and low dose intraperitoneal injection of streptozocin/Male Wistar rats/10 weeks | Assessed: 4/5 = weight gain, FBG, TG, HDL-C. Met: 3/5 = Reduced FBG and TG and increased HDL-c. Reduced insulin levels, insulin resistance (IR) and ISI | Upregulation of Carboxylesterase and retinal guanylate cyclase 2 precursors. Downregulation of IgG, carnitine acetyltransferase, tubulin beta 5, and Gan Lu sugar binding protein C. protein tyrosine kinase, beta glucosidase | 1 | 1 | No | No | No | Liu and Shi, (2019) |

(Continued on following page)
| S. No | Polyherbal combination | Model/animal/treatment duration | Parameters assessed: 5 = glucose/FBG, TG, HDL-C, BP and central obesity (weight, BMI, HC and WC). Parameters met: BMI [WC, HC], BP, HDL, TG, FBG. Additional: TC, LDL | Other parameters related to MetS | Score of study MetS parameters assessed >3 = 1; ≤3 = 0 | Score for effects (3/5: Good) = score 1; <3/5 (not so good) = score 0 | Concentration given | Quality control | Chemical classification | References |
|-------|------------------------|-------------------------------|----------------------------------------------------------|---------------------------------|------------------------------------|---------------------------------|----------------|-------------------|-------------------|------------------|
| 20    | SCH: Pharbitish semen, Trogopterorum fuses, Cyperin Rhizoma (2:1:1) | HFD mouse model, 3T3-L1 and HepG2 cells/Male C57BL/6J mice/15 weeks | Assessed: 3/5 = Glucose and insulin, TG and TC levels. Parameters met: 3/5 = Reduced glucose levels and insulin levels (HOMA-IR index reduced), Reduced TC and TG. Regulated adipogenic gene expression, proteins involved in energy metabolism (in maturated 3T3-L1 cells), Increased phosphorylated AMP activated protein, as well as attenuated insulin resistance and hepatic steatosis, Improved glucose facilitation by GLUT2 externalization. In FFA-induced steatotic HepG2 cells decreased ALT and AST. Increased serum free T4 and T3 hormones | 0 | 1 | Yes | No | No | Lim et al. (2019) |
| 21    | Marjoram and chicory Marjoram dry leaves (Origanum majorana) and chicory dry leaves (Cichorium intybus) (1: 5 w/v in water) | HFD/female SD abino rats/4 weeks | Parameters assessed: 3/5 = Body weight gain, TG, HDL-c (Additional: TC, LDL-c, VLDL-c, adipose tissue weight). Parameters met: 3/5 = lowered weight gain (Adiposity index and FER), reduced TG, and increased HDL-c; Adipose tissue weight, TC, LDL-c, VLDL-c also reduced decreased ALT and AST. increased serum free T4 and T3 hormones | 0 | 1 | Yes | No | No | A. Ahmed et al. (2009) |
| 22    | Gambihwan (GBH1): Ephedrae Herba; Coicis semen; Menthae herba Gypsum; Alismatis Rhizoma; Craetaegi fructus; Arecae semen; Hordei fructus germinatus GBH2: Ephedrae herba; Coicis semen; Typhae pollen; Castaneae semen; Siromeni Caulis et Rhizoma; Scutellariae radix | Model: HFD-induced obese mice/C57BL/6 mice (4 weeks old/ 8 weeks | Assessed: 4/5 = Body weight Glucose, TG, HDL Met: 2/5 = Reduced body weight, FBG, insulin levels, Improved OGTT. No effect on HDL. Decrease in TC, liver and fat weight inflammatory and hepatic enzyme levels diminished, suppressed lipid accumulation | 1 | 0 | Yes | No | No | Jang et al. (2018) |
| 23    | Sylimarin, Schisandrae Fructus, Craetaegus Fructus and Momordica charantia (1:1:1:1) | HFD and Cell lines: 3T3-L1, Caco-2 and HepG2 cell line/D578/6 male mice/8 and 12 weeks | Assessed: 4/5 = body weight (fat pad weight to body weight ratio), liver weight to body weight ratio; TG, glucose, insulin, TC, LDL-c also assessed. Met: 1/5 = reduced diet-induced increase in body weight and fat pad mass, reduced diet-induced increase in liver weight, liver lipid, and plasma lipid. No Effect on glucose and insulin, reduced liver TC and TG. Reduced TC and LDL-c Improved Plasma adiponectin level, reduced inflammation (reduced mac-3 expression) in liver. Inhibitory effects on 3T3-L1 preadipocytes differentiation inhibited the glucose uptake Inhibited fatty acid uptake prevented the cholesterol uptake | 0 | 0 | Yes | Yes | Yes | Wat et al. (2018) |

(Continued on following page)
### TABLE 3 (Continued)

Summary of meta-analysis of Polyherbal combinations used in animal-based models of Metabolic Syndrome.

| Concentration | Quality control | Chemical classification | References |
|---------------|-----------------|-------------------------|------------|
| control | Low dose STZ-induced diabetic Rat | insulin resistant, high fat diet, ABPA, atherosclerosis, AIP, adiponectin deficiency | Park et al. (2008) |
| glucose/FBG, TG, HDL-C, BP | Yes | Glucose | Lee et al. (2015a) |
| lipid profile | Yes | Lipid profile | Sung et al. (2014) |
| waist, hip | Yes | Waist, hip | Amin et al. (2015a) |

From the effect point of view, different combinations were identified as very effective in animal-based studies. They included combination of *Curcuma longa*, *Salacia reticulata*, *Gymnema sylvestre*, *Emblica officinalis*, *Terminalia chebula* (Thota et al., 2014), *Glycyrhizae uralensis* Fischer, *Rheum undulatum* Linne, *Prunus persica* Linne, *Cinchona camissa* Presl and *Natrii Sulfas* (Sung et al., 2014), *Rhizoma coptidis*, *Radix scutellariae*, *Cortex phellodendri* and *Fructus gardeniae* (Li et al., 2013), Red ginseng and *Polygoni Multiflori Radix* (Kho et al., 2016) and modified lingguizhugan decoction (Yao et al., 2017a). These combinations modulated all the five parameters of MetS including reduction in body weight/obesity, BP, TG, and fasting blood glucose (FBG) and increase in HDL. Additionally, combination of soybean meal and probiotics (Bifidobacterium longum) (Mounts et al., 2015), Fu Fang Zhen Zhu Tiao Zhi formula (Hu et al., 2014), *Artemisia iwayomogi* and *Nigella Sativa* (Amin et al., 2015a) and mixed extracts of *Artemisia iwayomogi* and *Curcuma longa* (Lee et al., 2015a) improved 4/5 MetS parameters and can be further considered for clinical trials.

These studies however exhibited certain limitations. For example, Lee et al. (2015a), comprehensively studied effect of *Artemisia iwayomogi* and *Curcuma longa* extract on metabolic markers along with fine mechanistic details but did not use positive controls in their study. Similarly, Yao et al. (2017a) did not use positive controls in their study when studying effect of modified Lingguizhugan decoction (MLD) and only selected one dose for intervention. Hence, dose dependent effect couldn’t be assessed. Besides, they did not study the effect mediated by MLD alone and only showed results of MLD with dietary restriction and exercise; additional group of MLD should have been added for confidently claiming the effect of MLD in the study. Amin et al., presented their findings comprehensively about use of combined *Curcuma longa* and *Nigella sativa* in MetS models but despite of mention of measuring body weight fortnightly, there were no results about effect on body weight (Amin et al., 2015a).

Some studies showed reduced effect on Met S parameters, but their focus was more on mechanistic details. For instance, study by Gao et al. (2015) on effect of Erchen decoction (ECD) exhibited effect on 3 parameters of MetS including FBG, TG and body weight and abdominal circumference. One of the appreciable aspects of this study is that the researchers reported abdominal circumference and body weight simultaneously. Limited animal studies consider abdominal circumference, which is the actual predictor of MetS. Additionally, molecular mechanisms of ECD on diabetic parameters have been elaborated at genetic level, where expression of CDK5 regulatory subunit associated protein 1 modulation of MetS parameters. Studies which were able to modulate 4-5 parameters were considered as very effective, whereas studies that modulated three or less than 3 parameters were marked as not so good. This, however, does not reflect on the quality of review. For the quality of review, we devised an 8-question checklist and marked one point for meeting the criteria and 0 for no meeting the criteria. The overall score was 8.
TABLE 4 | Qualitative scoring of studies on polyherbal combinations used in animals of Metabolic Syndrome models.

| References          | Dosage of herb provided | Components and rationale for dosing | animal ethical approval, Yes = 1, No = 0 | Endothanasia protocol mentioned/ followed, Yes = 1, No = 0 | Model validated for MetS | Positive control used, Yes = 1, No = 0 | Met S parameters assessed >3 = 1; <3 = 0 | Effect 3/5 parameters met = good effect (score 1); <3/5 = not so good (score 0) | Total score for Quality, 8 | Link                                                                 |
|---------------------|-------------------------|-------------------------------------|------------------------------------------|-----------------------------------------------------------|--------------------------|----------------------------------------|------------------------------------------|--------------------------------------------------------------------------------|-------------------------------|--------------------------------------------------------------------------------------------------|
| Thota et al. (2014) | 1                       | 1                                   | 1                                        | 1                                                         | 1                        | 0                                      | 1                                        | 1                                                                              | 7                             | https://citeseerx.ist.psu.edu/viewdoc/download?doi=10.1.1.637.1098&rep=rep1&type=pdf                |
| Sung et al. (2014)  | 1                       | 1                                   | 1                                        | 1                                                         | 0                        | 1                                      | 1                                        | 1                                                                              | 7                             | https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4193160/                                      |
| Li et al. (2013)    | 1                       | 1                                   | 1                                        | 1                                                         | 1                        | 1                                      | 1                                        | 1                                                                              | 7                             | https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3695866/                                       |
| Kho et al. (2016)   | 1                       | 1                                   | 1                                        | 1                                                         | 1                        | 1                                      | 1                                        | 1                                                                              | 7                             | https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4784406/pdf/12906_2016_Article_1053.pdf          |
| Yao et al. (2017a)  | 1                       | 1                                   | 1                                        | 1                                                         | 1                        | 1                                      | 1                                        | 1                                                                              | 7                             | https://link.springer.com/article/10.1186/s12906-017-1557-y                                  |
| Amin et al. (2015a) | 1                       | 1                                   | 1                                        | 1                                                         | 1                        | 1                                      | 1                                        | 1                                                                              | 7                             | https://journals.lww.com/cardiovascularpharm/Abstract/2015/02000/Coadministration_of_Black_Seeds_and_Turmeric_Shows.12.aspx |
| Mounts et al. (2015) | 1                       | 1                                   | 1                                        | 1                                                         | 1                        | 1                                      | 1                                        | 1                                                                              | 7                             | https://www.ncbi.nlm.nih.gov/pmc/articles/PMC493467/                                         |
| Lee et al. (2013b)  | 1                       | 1                                   | 1                                        | 1                                                         | 1                        | 1                                      | 1                                        | 1                                                                              | 7                             | https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4698622/                                         |
| Hu et al. (2014)    | 1                       | 1                                   | 1                                        | 1                                                         | 1                        | 1                                      | 1                                        | 1                                                                              | 7                             | https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3943467/                                         |
| Gao et al. (2015)   | 1                       | 1                                   | 1                                        | 1                                                         | 1                        | 1                                      | 1                                        | 0                                                                              | 7                             | https://www.hindawi.com/journals/ecam/2015/501272/                                           |
| Kaur and C (2012)   | 1                       | 1                                   | 1                                        | 1                                                         | 1                        | 1                                      | 1                                        | 1                                                                              | 7                             | https://www.ncbi.nlm.nih.gov/pmc/articles/PMC317057/                                         |
| Tan et al. (2013)   | 1                       | 1                                   | 1                                        | 1                                                         | 1                        | 1                                      | 1                                        | 1                                                                              | 7                             | https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3588405/pdf/ECAM2013-306738.pdf                   |
| Wei et al. (2012)   | 1                       | 1                                   | 1                                        | 1                                                         | 1                        | 1                                      | 1                                        | 0                                                                              | 6                             | https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0075560                     |
| Azushima et al. (2013) | 1             | 1                                   | 1                                        | 1                                                         | 1                        | 1                                      | 1                                        | 0                                                                              | 6                             | https://journals.plos.org/plosone/article/comments?id=10.1371/journal.pone.0075560          |
| Li et al. (2015)    | 1                       | 1                                   | 1                                        | 0                                                         | 1                        | 1                                      | 1                                        | 1                                                                              | 6                             | https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0122024                   |
| Chen et al. (2017)  | 1                       | 1                                   | 1                                        | 0                                                         | 1                        | 1                                      | 0                                        | 1                                                                              | 6                             | https://pubs.rsc.org/en/content/articlepdf/2017/ra/c7ra09779dSupplementary reference: http://www.rsc.org/suppdata/c7/r/a/c7ra09779d/c7ra097779d1.pdf |
| Leong et al. (2013) | 1                       | 1                                   | 1                                        | 1                                                         | 1                        | 1                                      | 0                                        | 1                                                                              | 6                             | https://pdfs.semanticscholar.org/870a/eb206240998b3209e0a18e2cd87cf343ae750.pdf               |
| Tan et al. (2011)   | 1                       | 1                                   | 1                                        | 1                                                         | 1                        | 1                                      | 1                                        | 0                                                                              | 6                             | https://www.researchgate.net/publication/47447592_Chinese_herbal_extracts_SK0506_as_a_potential_candidate_for_the_therapy_of_the_metabolic_syndrome |

(Continued on following page)
TABLE 4 (Continued) Qualitative scoring of studies on polyherbal combinations used in animals of Metabolic Syndrome models.

| References | Dosage of herb provided | Components and rationale for dosing | animal ethical approval, Yes = 1, No = 0 | Euthanasia protocol mentioned/ followed, Yes = 1, No = 0 | Model validated for MetS | Positive control used, Yes = 1, No = 0 | MetS parameters assessed ≥ 3 = 1; < 3 = 0 | Effect 3/5 parameters met = good effect (score 1) < 3/5 = not so good (score 0) | Total score for Quality, 8 Link |
|------------|-------------------------|-------------------------------------|------------------------------------------|--------------------------------------------------------|-------------------------|--------------------------------------|--------------------------------|--------------------------------------------------------------------|-----------------------------|
| 19 Liu and Shi, (2015) | 1                       | 0                                  | 0                                        | 0                                                      | 0                       | 0                                    | 0                                    | 1                                                                  | 5 https://pubmed.ncbi.nlm.nih.gov/25902033/ |
| 20 Lim et al., (2019) | 1                       | 1                                  | 0                                        | 0                                                      | 0                       | 0                                    | 0                                    | 1                                                                  | 5 https://www.nature.com/articles/s41598-019-45099-x |
| 21 A. Ahmed et al. (2009) | 1                       | 0                                  | 0                                        | 0                                                      | 0                       | 0                                    | 0                                    | 1                                                                  | 5 http://citeseerx.ist.psu.edu/viewdoc/download?doi=10.1.1.321.1771&rep=rep1&type=pdf |
| 22 Jang et al., (2018) | 1                       | 1                                  | 0                                        | 0                                                      | 0                       | 0                                    | 0                                    | 1                                                                  | 4 https://www.hindawi.com/journals/eam/2018/5614091/ |
| 23 Wat et al., (2018) | 1                       | 1                                  | 0                                        | 0                                                      | 0                       | 0                                    | 0                                    | 1                                                                  | 4 https://pubmed.ncbi.nlm.nih.gov/29655677/ |
| 24 Park et al., (2009) | 0                       | 0                                  | 0                                        | 0                                                      | 0                       | 0                                    | 0                                    | 1                                                                  | 2 https://www.researchgate.net/publication/288976056_Effects_of_herbal_complex_on_blood_glucose_in_streptozotocin-induced_diabetic_rats_and_in_mice_model_of_metabolic_syrnome |

Some studies design was flawed and therefore the effects could not be validated. Aims of the study were not clearly written in the write-up. Similarly, a combination of nutraceuticals with dietary interventions very efficiently reflected the improvement in MetS parameters to an extent that the patients no longer fulfilled the MetS criteria after treatment. Nevertheless, with further research, this combination could be considered for future studies.
| S. No | Sample size | Population | Intervention/ Phenomenon of interest | Study Design | Evaluation [MetS parameters assessed out of 5] | Evaluation Outcome (Parameters met) | Other targets | Research Type (quantitative/ qualitative) | References | Concentration reported | Quality control reported | Chemical analysis reported |
|-------|-------------|------------|--------------------------------------|--------------|---------------------------------------------|-----------------------------------|--------------|----------------------------------------|------------|-------------------------|--------------------------|-----------------------------|
| 1     | 100 (50 control, 50 treatment) | Subjects with MetS complicated with MAU | Yiqi Huazhuo Gushen herbal formula (Orpica chinensis, Pollen typhae, the rhizome of oriental water plantain, Mung bean peel, Serissa serissoides, Radix Aconiti lateralis praeparata)+ valsartan | Double-blinded and placebo-controlled | 5/5: BMI, FPG, 2hPG, HbA1c, (HOMA-IR), SBP and DBP, MABP, TC, TG, LDL, HDL | 4/5: reduced BMI, WHR, SBP, MAP, FPG, 2hPG, HbA1c, reduced TG, increased HDL, LDL-c | Quantitative | Reductions in MAP, UACR, 2hTP and urinary β2 microglobulin | Tian-zhan et al. (2019) | Yes | No | No |
| 2     | 60 (treatment = 30; control group = 30) | Subjects with MetS | Yiqi Huaju Qingli Formula with western medicine: Radix Astragali, Rhizoma Coptidis, Pollen Typhae, Artemisiae Rhizoma Alismatis, Testa Vignae Radiatae, Serissa Japonica, and Radix Aconiti Lateralis Preparata | Randomized placebo-controlled | 5/5: BMI, WC, WHR, FPG, 2hPG, HbA1c, homeostasis model assessment for insulin resistance (HOMA-IR), TC, LDL, TG, HDL, BP | 4/5: decreased BMI, WC, WHR, FPG, 2hPG, HbA1c, increased HDL | Quantitative | reduced Urinary MA, UACR | Wang et al. (2013) | Yes | No | No |
| 3     | 75 (Sesame + vitamin E = 25, Sesame = 25; Sunflower oil = 25) | Subjects with MetS (aged 30–70 years) | Sesame oil and vitamin E | Randomized, single-blind controlled | 4/5 = dietary intake, BP, FBG, serum insulin, TC, TG, HDL | 4/5 = reduced TC, TG, FBG, HOMA-IR, SBP, DBP, increased HDL-c | Quantitative | MDA, Hs-CRP, | Farajbakhsh et al. (2019) | Yes | No but it was recruited from company | No |
| 4     | 250 (63 per group; 4 groups) | Subjects with MetS | Curcuma longa and Nigella sativa | Double blind randomized controlled | 5/5: BMI, BF %, WC, HC, BP, TC, HDL-c, LDL-c, TG, FBG | 3/5: reduced BMI (weight, HC, BF%), FBG, TG, TC, LDL-c | Quantitative | CRP, | Amir et al. (2015b) | Yes | No | No |

(Continued on following page)
| S. No | Sample size | Population | Intervention/Phenomenon of interest | Study Design | Evaluation [MetS parameters assessed out of 5] | Evaluation Outcome (Parameters met) | Research Type (quantitative/qualitative) | Other targets | References | Concentration | Quality control reported | Chemical analysis reported |
|-------|--------------|------------|-----------------------------------|--------------|--------------------------------------------|--------------------------------------|----------------------------------------|--------------|------------|---------------|--------------------------|-----------------------------|
| 5     | N = 116 divided in 5 different groups | Type 2 diabetic subjects with MetS | Diabecon, (Momordica charantia, Swertia chirata, Gymnema sylvestre, Trigonella foenumgraecum, Phumbago zeylanica, Eugena jambolana, Aegle marmelos, Terminalia chebula, Terminalia baterica, Emblica officinalis, Curcuma longa, Pterocarpus marsupium, Berberis aristata, Cytella colocynthis, Cyperus rotundus, Piper longum, root of Piper longum, Zingiber officinale, and Asphaltum punjabinum) | Double-blinded and placebo-controlled | 4/5: BMI, FBG, TC, TG, LDL, HDL, VLDL | 3/5: reduction in FBG, reduced TC, LDL, TG, increase HDL | Quantitative | reduction in uric acid, creatinine. Maintained LFTs (SGOT and SGPT) | Yadav et al. (2014) | Yes | No | No |
| 6     | 21 Subjects with MetS (17–70 years) | N/A | Modified Lingzhu Decoction (MLD)+ weekend fasting: (MLD = Poria, Ramulus Cinnamomion, Rhizoma Atractylodis Macrocephalae, and Radix Glycyrrhizae) | N/A | 5/5: FPG, 2-h post-prandial blood glucose, fasting serum insulin (FINS), BP, BMI, WC, HOMA-IR, TG, TC, LDL-C, HDL-C | 3/5: reduced FPG, HOMA-IR, PG, SBP, BMI, WC, LDL-C, decreased significantly | Quantitative | Yang et al. (2014b) | Yes | No but Pharmaceutical company provided it | No |
| 7     | 450 (treatment = 225, Metformin = 225) | Type 2 diabetes | Dahuang Huanglian Xiexin Decoction (JTTZ): Aloe vera, Coptis chinensis, Rhizoma Anemarrhenae, red yeast rice, Momordica charantia, Salvia miltiorrhiza, Schisandra chinensis, and dried ginger | Positive-Controlled, Open-label | 3/5: BMI, weight, WC, HC HbA1c, Total cholesterol, TG, FPG, 2 h PG, HOMA-IR, (HOMA-β), TC, LDL-C | 3/5: decreased HbA1c, FPG levels, TG and LDL-C levels, BMI, WC, HC | Quantitative | Yu et al. (2018) | No, established formula. Dose and duration given | Yes | Yes |

(Continued on following page)
| S. No | Sample (size) | Population | Intervention/Phenomenon of interest | Study Design | Evaluation [MetS parameters assessed out of 5] | Evaluation Outcome (Parameters met) | R | Research Type (quantitative/qualitative) | Other targets | References | Concentration | Quality control reported | Chemical analysis reported |
|-------|---------------|------------|-----------------------------------|--------------|---------------------------------------------|-----------------------------------|---|-------------------------------------|----------------|------------|---------------|------------------------|--------------------------|
| 8     | 30 (placebo = 15; treatment = 15) | Subjects with MetS Nutraceuticals (Armolipid Prev, Rottapharm, Monza, Italy) + dietary intervention | Randomized, controlled, double-blind, parallel-group, single-centre | 5/5: BMI, FBG, TG, HDL, SBP, DBP, TC, LDL | 3/5: Reduce SBP and DBP, TG, LDL-C, TC, Increase HDL. MetS prevalence reduced from 15 to 5 | Quantitative | N/A | | | Rozza et al. (2009) | registered drug so concentration may be in fixed preparation. Authors have not mentioned | No | No |
| 9     | 100 (treatment = 50; placebo = 50) | Subjects with MetS Attiix® Supplement Containing Chlorogenic Acid and Luteolin | Randomized, Double-Blind | 4/5: Body weight and BMI, FBG, HbA1c, Insulin resistance, pancreatic b cell function (HOMA-IR), TC, TG, LDL-C, HDL | 3/5: Weight and BMI, improved Glycemic variables (HbA1c, HOMA-IR, and HOMA-Iβ), reduced TC, TG, and LDL-C | Quantitative | | | | Castellino et al. (2019) | No (prepared supplement-registered) | No | No |
| 10    | 117 (treatment = 59; placebo = 58) | Subjects with MetS Curcuminoids (95% curcuminoids, of which at least 70% is curcumin) + piperine to enhance bioavailability | Randomized double-blind placebo-controlled | 2/5: weight and BP | 2/5: reduction in Weight, height, SBP, DBP | Quantitative | SOD, MDA, hs-CRP, | | | Panahi et al. (2015) | Patented ratio is mentioned but exact concentration not given | No | No |
| 11    | 100 (placebo = 50; treatment = 50) | Subjects with MetS Curcuminoids (95% curcuminoids, of which at least 70% is curcumin) + piperine to enhance bioavailability | Randomized double-blind placebo-controlled parallel-group | 2/5: TC, LDL-C, HDL-C, TG, LDL, lipoprotein and non-HDL-C | 2/5: Reduced TG, elevated HDL-C, reduced TC, LDL-C, non-HDL-C | Quantitative | | | | Panahi et al. (2014) | 1000 mg curcuminoids per day with 10 mg piperine | No | No |
| 12    | 50 (placebo = 26; treatment = 24) | Subjects with MetS Red yeast rice and olive extract | Double blind placebo controlled randomized | 5/5 | | Quantitative | CK elevation, ApoA1, ApoB, HbA1c and oxLDL | high levels of CRP, FFA and PAI, t-PA was low | | Verhoeven et al. (2015) | commercially available food supplement | Yes | Yes |
| 13    | 30 healthy males; 45 obese divided into two groups | Centrally Obese men Yiqi Sanju Formula | Randomized controlled | 2/5 = Insulin Resistance, BMI | 2/5 = HOMA-IR and BMI reduced | Quantitative | | | | He et al. (2007) | | |

(Continued on following page)
TABLE 5 | (Continued) Summary of meta-analysis of polyherbal combinations used in Clinical studies in patients with MetS according to SPIDER model, concentration, quality control and chemical classifications reports.

| S. No | Sample (size) | Population | Intervention/ Phenomenon of interest | Study Design | Evaluation [MetS parameters assessed out of 5] | Evaluation Outcome (Parameters met) | Research Type (qualitative/ quantitative) | Other targets | References | Concentration | Quality control reported | Chemical analysis reported |
|-------|---------------|------------|-------------------------------------|--------------|-----------------------------------------------|-------------------------------------|--------------------------------------|-------------|------------|---------------|--------------------------|---------------------------|
| 14    | 106 (treatment = 54; placebo = 52) | Adult subjects with MetS | Red yeast rice, bitter gourd, chlorella, soy protein, and licorice | double-blinded study | 5/5 = BMI, BP, FBG, OGTT, TC, TGs, HDL, LDL | 2/5 = reduced TG, BP, TC, LDL-c | Quantitative | No changes in LFT (ALT, AST, ALK-P) and renal functions test (serum creatinine, urea nitrogen, uric acid) | Lee et al. (2012) | Yes | Not mentioned but manufactured | No |
| 15    | 100 (placebo = 46; treatment = 46) | subjects with MetS | Keishibukuryogan: Cinnamomi Cortex, Paeoniae Radix, Moutan Cortex, Persicae Semen, and Hoelen | controlled clinical trial with crossover design. Open labelled study; Quasi randomized | 5/5 = BMI, HDL, LDL, FBG, TC, TG, BP | 0/5 = Reduced HDL, LDL, TC, TG, BP | Quantitative | No changes in serum HDL, LDL, TC, TG, BP | Nagata et al. (2012) | Yes | No | No |

Abbreviations: 24hTP, 24 h total urinary protein; 2hPPG, 2 h post prandial glucose; AST, aspartate aminotransferase; ALT, alanine transaminase; ALP, alkaline phosphatase; BP, blood pressure; BMI, body mass index; CDKAL = CDK5 Regulatory Subunit Associated Protein 1 Like 1; CETP, cholesteryl ester transfer protein; CRP, C-reactive protein; FBG: fasting blood glucose; FFA, free fatty acid; GLUT-4, glucose transporter 4; HDL-C, high density lipoprotein; HFD, high fat diet; HOMA-IR, homeostatic model assessment for insulin resistance; ICAM-1, intercellular adhesion molecules; IRS-1, Insulin receptor substrate 1; KKAy, cross between diabetic KK and lethal yellow; LDL, low density lipoprotein; Monocyte chemoattractant protein-1; MAU/MA, microalbuminuria; MDA, malondialdehyde; NAFA, non-esterified fatty acids; NF-κB, Nuclear Factor kappa-light-chain-enhancer of activated B cells; PI3K, phosphoinositide 3-kinase; SREBP, sterol regulatory element-binding transcription factor; PPAR-y, Peroxisome proliferator-activated receptor gamma/alpha; SD Rats, Sprague Dawley rats; SGOT, Serum glutamic oxaloacetic transaminase; SGPT, Serum glutamic pyruvic transaminase; SOD, superoxide dismutase; TC, total cholesterol; TG, triglycerides; TNF, Tumor necrosis factor; vCAM-1, Vascular cell adhesion molecule 1; vCD3, very low density lipoprotein; UACR, urine creatinine albumin ratio; WC, waist circumference; WHR, waist hip ratio; WKy, Wistar Kyoto.
| References | Code | Addressed clearly focused question | Subjects to treatment groups randomised | Subjects and investigators “blind” | The treatment and control groups are similar at the start of the trial | The only difference between groups is the treatment under investigation | All relevant outcomes are measured in a standard, valid and reliable way | Dropped out before study completion | All the subjects are analysed in the groups to which they were randomly allocated | Where the study is carried out at more than one site, results are comparable for all sites | Link |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Wang et al., 2019 *(Tian-zhan et al., 2019)* | 1 1 1 1 1 1 1 1 0 1 2 | | | | | | | | | | | [https://www.ajol.info/index.php/tjpr/article/view/183342](https://www.ajol.info/index.php/tjpr/article/view/183342) |
| Wang et al. (2013) | 1 1 1 1 1 1 1 1 3 1 2 | | | | | | | | | | | [https://pubmed.ncbi.nlm.nih.gov/23743161/](https://pubmed.ncbi.nlm.nih.gov/23743161/) |
| Mazloomi et al., 2019 *(Farajbakhsh et al., 2019)* | 1 1 1 1 1 1 1 1 5 (8%) 1 2 | | | | | | | | | | | [https://pubmed.ncbi.nlm.nih.gov/31089253/](https://pubmed.ncbi.nlm.nih.gov/31089253/) |
| Amin et al. (2015b) | 1 1 1 1 1 1 1 3 1 2 | | | | | | | | | | | [https://www.sciencedirect.com/science/article/abs/pii/S0965229915000096?via%3Dihub](https://www.sciencedirect.com/science/article/abs/pii/S0965229915000096?via%3Dihub) |
| Wang et al. (2013) | 1 1 1 1 1 1 1 3 1 2 | | | | | | | | | | | [https://pubmed.ncbi.nlm.nih.gov/25102690/](https://pubmed.ncbi.nlm.nih.gov/25102690/) |
| Mazloomi et al. (2019) *(Farajbakhsh et al., 2019)* | 1 1 1 1 1 1 1 5 (6%) 1 2 | | | | | | | | | | | [https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6893885/](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6893885/) |
| Panahi et al. (2015) | 1 1 1 1 1 1 1 curcuminoids (9/59) placebo (8/58) | | | | | | | | | | | [https://pubmed.ncbi.nlm.nih.gov/25440375/](https://pubmed.ncbi.nlm.nih.gov/25440375/) |
| Verhoeven et al. (2015) | 1 1 1 1 1 1 1 1/25 from intervention group | | | | | | | | | | | [https://bmccomplementmedtherapies.biomedcentral.com/articles/10.1186/s12906-015-0576-9](https://bmccomplementmedtherapies.biomedcentral.com/articles/10.1186/s12906-015-0576-9) |
| Wang et al., 2007 *(He et al., 2007)* | 1 1 1 1 1 1 1 1 N/A 1 2 | | | | | | | | | | | [http://www.jcimjournal.com/EN/10.3736/jcim20070307](http://www.jcimjournal.com/EN/10.3736/jcim20070307) |
| Lee et al. (2012) | 1 1 1 1 1 1 1 2/54 (treatment) and 8/52 (placebo) | | | | | | | | | | | [https://pubmed.ncbi.nlm.nih.gov/22348456/](https://pubmed.ncbi.nlm.nih.gov/22348456/) |
| Nagata et al. (2012) | 1 1 1 2 2 2 2 1 1 1 2 | | | | | | | | | | | [https://www.hindawi.com/journals/ije/2018/9519231/](https://www.hindawi.com/journals/ije/2018/9519231/) |
small sample size, the magnitude of impact could not be extrapolated and needs to be studied further. Some clinical studies assessed only limited parameters of MetS and therefore in terms of effectiveness those combinations are considered as not so good. Nevertheless, that’s not completely true, because the authors did not measure the remaining parameters (He et al., 2007; Panahi et al., 2014; Panahi et al., 2015). Reason for this could be that the main objective of those studies was to explore additional mechanisms of MetS. For instance, Panahi et al. (Panahi et al., 2015) report curcuminoids to reduce 2 out of 5 MetS parameters because they assessed only BP and BMI. Their main finding was anti-inflammatory and antioxidant activities, whereas antidyshlipidemic effect was reported in their preceding study (Panahi et al., 2014).

The current review has certain limitations. One of the factors to be considered for future reviews should be to differentiate the polyherbal combinations according to different ethnicities and cultures in which the herb is famously used such as Asian, Chinese and Japanese traditional medicine. The current review can be used by researchers for identifying different polyherbal combinations by considering which herbs could simultaneously target many or all risk factors for MetS. For future studies some known anti-obesity and/or antihypertensive herbs shall be considered as an add-on with those polyherbal combinations that predominantly exhibited anti-hyperglycaemic and antidyshlipidemic effect, to be able to manage multiple MetS parameters simultaneously. This is one of the advantages of such reviews that researchers could identify the missing targets and add herb accordingly for future studies.

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