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Scoping review of the medicinal effects of *Eupolyphaga sinensis* Walker and the underlying mechanisms

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ABSTRACT

Ethnopharmacological relevance: Eupolyphaga sinensis Walker (ES) is an insect widely used in traditional East Asian medicine known to exhibit clinical effects on various pathological conditions. Overall, ES is a useful medicinal insect that can treat various diseases, including cancer and immune diseases. However, further mechanistic studies based on its therapeutic effects in clinical settings are required.

Aim of the study: We aimed to evaluate the current research landscape and diseases associated with ES to synthesize the clinical value of ES based on the associated diseases and underlying therapeutic mechanisms.

Materials and methods: Embase and PubMed databases were searched for experimental studies that evaluated the therapeutic efficacy or underlying mechanisms of ES until May 2021. The evidence for each study was summarized using a narrative synthesis approach. Studies on extracted or dried whole ES and ES-derived compounds were quantitatively analyzed by year and disease type. Meanwhile, the overall research trend was confirmed for studies on ES-containing prescriptions by visualizing the disease type analysis.

Results: A total of 151 studies were identified, of which 51 were included in our review. There were 14 studies on extracted or dried whole ES, 15 on ES-derived compounds, and 22 on ES-containing prescriptions. ES was most commonly used for cancer-related diseases, followed by those related to endocrine function and immunity. ES regulates the cell cycle, tumor suppressor genes and proteins, immune-related biomarkers, and antioxidant molecules.

Conclusions: Overall, ES is a beneficial medicinal insect that can treat various diseases, including cancer and immune diseases. However, further mechanistic studies based on its therapeutic effects in clinical settings are required.

1. Introduction

Traditional East Asian medicine (TEAM) has been used for thousands of years in East Asian countries and is considered safe (Fang et al., 2018; Tang et al., 2018; Yang et al., 2015). TEAM uses natural medicinal resources obtained from plants, minerals, animals, and insects (Feng et al., 2009). Although plants are the most commonly used materials in clinical practice and research (Colalto, 2018), medical interest in insects has recently increased (Zhan et al., 2016). There are approximately 300 species of medicinal insects described in the literature on TEAM (Feng et al., 2009) including those frequently used in herbal medicine prescriptions such as *Vespae nidus, Mylabris, Agkistrodon, Bufonis venenum, Hirudo, Tabanus, Scolopendra, Eupolyphaga, Scorpiones*, and *Gekko gecko* (Hwang et al., 2021; Soltan-Alinejad et al., 2021; Wei et al., 2019).

Eupolyphaga sinensis Walker (ES), also called *Steleophaga plancyi* (Boleny), belongs to the family *Corydiidae* (Blattodea) and is widely distributed in Southeast Asian countries, including Thailand, India, Malaysia, and China (Feng et al., 2009; Xie et al., 2020; Zhang et al., 2014). ES has long been used as a food source as they are a rich in proteins, vitamins, essential amino acids, minerals, and essential fatty acids (Zhang et al., 2014) and as a drug in TEAM (Liu et al., 2019; Zhang et al., 2014). ES is traditionally known as a drug that regulates blood circulation by removing "static blood," a pathological product of blood stagnation that may become a pathogenic factor (Yang et al., 2011; Zhu

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et al., 2021). ES has been tested as a treatment for various conditions, such as cancer (Zhan et al., 2016), as well as for its role in blood circulation and thrombosis (Xie et al., 2001), immunity (Liu et al., 2019), and bone metabolism (Qi et al., 2013). Recently, Hwang et al. (2021) reported ES, together with *Hirudo* and *Scolopendra*, as toxic animals showing clinical efficacy for endometritis. However, to date, no studies have comprehensively summarized and analyzed the overall therapeutic effects of ES and its underlying mechanisms of action.

Therefore, we conducted a scoping review of recent experimental studies on ES to synthesize the current research landscape and describe the clinical value of ES.

2. Materials and methods

2.1. Methodology

For this scoping review, the method was modified according to the study objective of Levac et al. (2010) that was based on the methodology of Arksey and O'Malley (2005) who proposed a five-stage framework for conducting scoping reviews including: "identifying the research questions; " "identifying relevant studies; " "study selection; " "charting the data; " and "collating, summarizing, and reporting the results." We followed these stages.

This review aimed to identify the diseases treated with ES and its mechanisms of action. We reviewed the literature on ES, including studies on cell and animal models and clinical studies that used ES for medicinal purposes.

2.2. Literature search strategy

We searched the Embase (https://embase.com), and PubMed (https://pubmed.ncbi.nlm.nih.gov/) databases for articles on ES published until May 7, 2021. The search was performed by combining the following search terms with the appropriate search formula for each database: "*Eupolyphaga sinensis* Walker," "*Steleophaga plancyi*," "*Steleophaga plancyi* boleny," "*Eupolyphaga*," "*Polyphaga plancyi* bolívar," or "Steleophaga" (Supplementary Table S1). Our search did not have any language, article type, or study design restrictions.

2.3. Study selection

Based on the research question of this scoping review, the inclusion and exclusion criteria of the analyzed literature were established by discussion among the authors. We included experimental studies (1) on extracted or dried whole ES (ES-Wh), ES-derived compounds (ES-Cp), or ES-containing prescriptions (ES-Rx); (2) involving cell and animal models; and (3) involving human-based primary research to evaluate the effectiveness of ES and its mechanism of action. The exclusion criteria were: (1) studies without information on the effectiveness or mechanism of action of ES; (2) secondary studies using existing data (e.g., review or commentary), studies with results that were difficult to confirm, such as conference abstracts, or those that have been withdrawn from publication for some reason; (3) written in a language other than English, Chinese, or Korean; and (4) studies without availability of full-text material, despite the researchers' efforts to reach the corresponding author. One reviewer (B.S. Kim) screened and identified all records in advance to determine inclusion eligibility, which were confirmed by two other authors (J.Y. Park and S.Y. Kim). Any disagreements were resolved by discussion among the three reviewers (B.S. Kim, J.Y. Park, and S.Y. Kim).

2.4. Data extraction and synthesis

All data were extracted by a single reviewer (B.S. Kim) into a predetermined form using Microsoft Excel (Microsoft Corp., Redmond, WA, USA) and then confirmed by two authors (J.Y. Park and S.Y. Kim). Disagreements regarding data extraction were resolved through discussion among the authors.

In clinical practice, ES is provided to patients as decoctions, granules, or powders, and is generally mixed with other crude herbs; however, it is difficult to know the efficacy of ES alone. In order to confirm the independent efficacy of ES, the dried ES or ES extracted with water or other solvents is used experimentally. Each drying and extraction methods using different solvents have the potential to act pharmacologically different, but all of them can confirm the efficacy of ES using whole ES. Recently, experimental studies using only specific compounds of ES are being conducted for pharmaceutical research. Since the three types of ES (ES-Wh, ES-Cp, and ES-Rx) each have different properties, we analyzed these three types of ES separately.

Data on author information, year of publication, corresponding author's country of origin, language, and target disease were extracted from all studies. In addition, the specific method of administering ES and the results derived from each experiment were collected in a manner appropriate for the type of cell or animal based study. Information on clinical studies was collected based on the study design, ES prescription name, drug form (decoction, granules, or powder), dosage of each medical substance, formula dosage, administration route (oral or external), treatment duration, and control group details. Finally, based on the extracted data, the efficacy and mechanism reported in cell or animal studies for each disease according to the ES substance types (ES-Wh and ES-Cp), were summarized. Information on the diseases treated by ES was extracted based on the detailed disease names, and diseases were classified according to the International Classification of Diseases 11th Revision (ICD-11) guidelines. For ES-Rx, it was difficult to determine the independent efficacy or mechanism of ES because it is administered in combination with other substances. Therefore, the overall research trend was confirmed by visualizing the analysis of the disease type, which was part of the extracted data.

3. Results

3.1. Selection of included studies

According to our search strategy, 151 studies were screened and 55 duplicate documents were excluded. Based on the inclusion and exclusion criteria, 96 studies were identified. Studies that (1) did not use ES or ES-derived ingredients (n = 6), (2) were not related to efficacy or mechanisms in cells, animals, or humans (n = 34), and (3) were not original articles, such as reviews, commentaries, conference abstracts, or withdrawn articles (n = 12) were excluded. In addition, references of related published review articles were screened, and seven studies satisfying our inclusion criteria were identified. Finally, 51 articles comprising 14 studies on ES-Wh, 15 on ES-Cp, and 22 on ES-Rx were included in this review (Fig. 1).

3.2. Characteristics of included studies

The number of studies on ES has gradually increased since the 2000s. The number of published studies has also gradually increased, with 5, 13, and 16 publications from 2001 to 2005, 2006–2010, and 2011–2015, respectively. Since then, 11 studies have been published between 2016 and May 2021. Studies published from 2006 to 2021 account for 78.4% (n = 40) of all published ES studies. Fig. 2A shows the distribution of studies on ES-Wh, ES-Cp, and ES-Rx over the years. The studies were published mostly in English (n = 28, 55%) or Chinese (n = 23, 45%) (Fig. 2B). Of the 51 studies included, all were conducted in China, except for 5 conducted in Iran, Taiwan, France, Japan, and the United States (collaborative research in the United States and China) on ES-Rx (Fig. 2C).

Studies on ES-Wh, ES-Cp, and ES-Rx were first published in 1991, 1989, and 1993, respectively. The most published period for ES-Wh studies was 2011–2015 and for ES-Rx studies was 2006–2010. ES-Cp

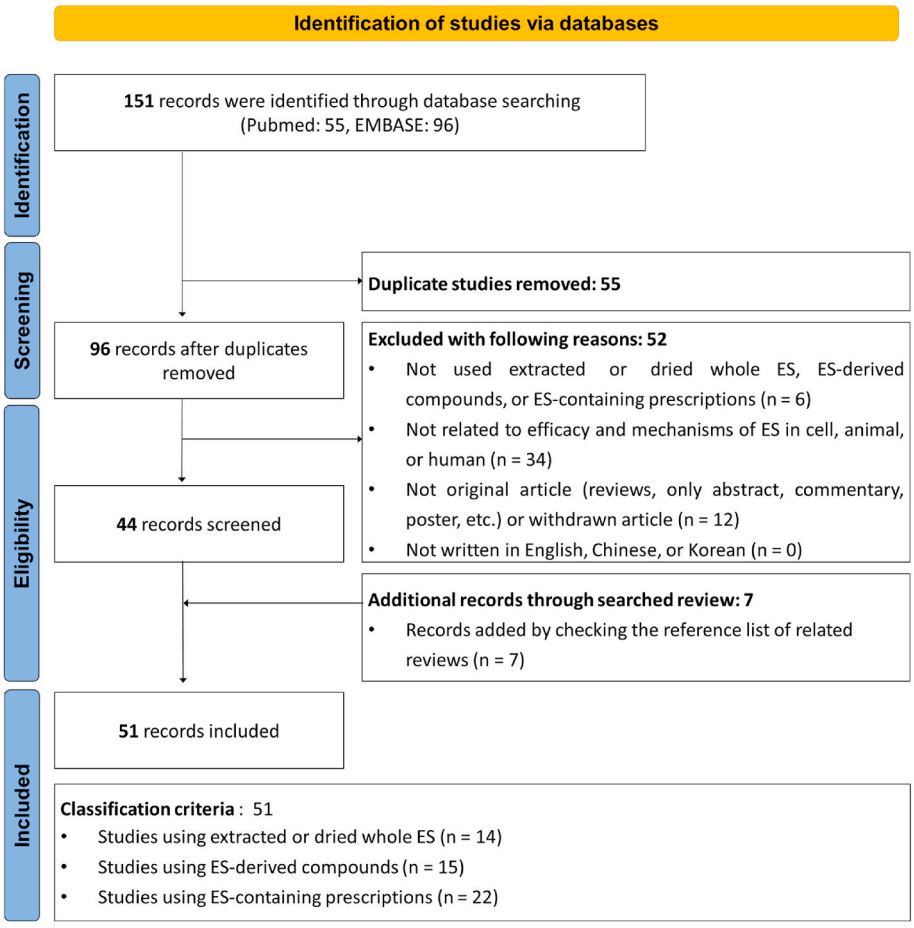

Fig. 1. Flow chart of the study selection process. ES: *Eupolyphaga sinensis* walker.

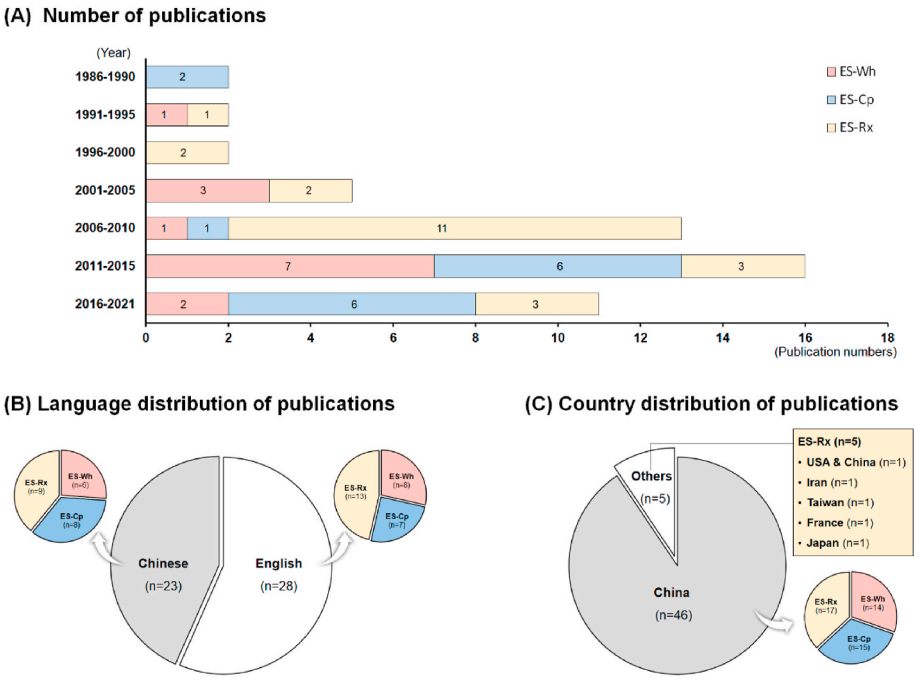

Fig. 2. General characteristics. (A) The number of publications at five-year intervals between 1986 and May 2021 was analyzed; (B) Language distribution of publications; (C) Country distribution of publications. ES: *Eupolyphaga sinensis* Walker; ES-Cp: ES-derived compounds; ES-Wh: extracted or dried whole ES; ES-Rx: ES-containing prescriptions.

studies have been actively conducted recently, with six publications each in 2011–2015 and 2016–2021.

3.3. Preparation methods of extracted or dried whole ES

In 14 ES-Wh studies, extraction with variable solvents was the most commonly used preparation method (n = 9), followed by drying (n = 2). The remaining three studies did not describe the preparation method (Tables 1 and 2). The most commonly used ES extraction methods were hot water (n = 4) and 70% ethanol (n = 4), followed by 95% ethanol (n = 1). Most of the studies used only a single preparation method, and few studies compared the efficacy of or differences in extract ingredients according to the different preparation methods. One study (Dai et al., 2014a) compared hot water extraction and 70% or 95% ethanol extraction, and reported that 70% ethanol extraction was more effective in inhibiting the proliferation of lung cancer cells than other extraction methods.

3.4. Therapeutic effects of ES and its related mechanisms

3.4.1. Diseases investigated by extracted or dried whole ES and ES-derived compounds studies

The diseases investigated in the included studies were categorized based on the ICD-11 guidelines as neoplasms; endocrine, nutritional, metabolic, immune system, circulatory system, haematopoietic system, musculoskeletal system, connective tissue, digestive system, genitourinary system, or skin diseases; and traditional medicine conditions (Fig. 3A).

Among these, studies on neoplasms were the most common (ES-Wh, n = 5; ES-Cp, n = 7) including liver (Cao et al., 2011; Ge et al., 2012; Han et al., 2009, 2011; Xie et al., 2020; Zhang et al., 2014), lung (Dai et al., 2014a; Wang et al., 2013), bone marrow (Dai et al., 2014b), and breast (Zhan et al., 2016) cancer. Studies using various cancer cell lines were also identified (Jiang et al., 2012; Zhu et al., 2021). The second most studied disease category was immune-related diseases (ES-Wh, n = 2; ES-Cp, n = 2), focusing on overall (Liu et al., 2012, 2019; Tang et al., 2010) and rheumatoid arthritis-related (Ni et al., 2016) immune function. Studies on endocrine-related diseases (ES-Wh, n = 1; ES-Cp, n = 2) mainly involved hyperlipidemia (Shan et al., 2020; Wang, 2020; Wang et al., 1991). Studies on diseases of the circulatory system included three ES-Cp studies on antithrombotic function (Yang et al., 2011), cardiac ischemia (Nong et al., 1989), and cardiac pump function (Yang et al., 1989) (Fig. 3B).

3.4.2. Extracted or dried whole ES and its related mechanisms in animal and cell studies

Among the studies performed with ES-Wh, neoplasm studies were the most frequent (n = 5), with three studies (Dai et al., 2014b; Zhan et al., 2016; Zhang et al., 2014) involving both cells and animals, one cell study (Dai et al., 2014a) and one animal based study (Ge et al., 2012) (Tables 1 and 2).

Of the five neoplasm studies, two were conducted on hepatocellular carcinoma (Ge et al., 2012; Zhang et al., 2014), and one each on breast cancer (Zhan et al., 2016), chronic myeloid leukemia (Dai et al., 2014b), and lung cancer (Dai et al., 2014a). All animal studies (n = 4) used a xenotransplantation model, and ES-Wh treatment effectively reduced tumor weight. Furthermore, ES-Wh increased spleen and body weights in the hepatocellular carcinoma animal model (Ge et al., 2012; Zhang et al., 2014), and Ge et al. (2012) reported that ES-Wh increased expression of immune-related factors (e.g., interferon-gamma, tumor necrosis factor-alpha) and apoptosis-related factors (caspase and B cell lymphoma-2 protein associated X protein [Bax]). In addition, Dai et al. (2014a) reported the inhibitory effects on proliferation of A549 lung cancer cells. The four neoplasm cell studies (Dai et al., 2014a, 2014b; Zhan et al., 2016; Zhang et al., 2014) suggested that ES-Wh inhibits cell proliferation/differentiation, the cell cycle, and angiogenesis/migration (invasion). Although the findings relating to the cell cycle are inconsistent (Dai et al., 2014b; Zhang et al., 2014), a general tendency of cell cycle arrest was observed (Table 2).

Two animal studies on immune system diseases showed that ES-Wh regulates immunity, oxidative stress, and inflammation-related factors by improving the spleen and thymus indices (Liu et al., 2019; Tang et al., 2010) (Table 1). Two cell studies on the haematopoietic system were conducted on bone marrow mesenchymal stem cells, to confirm the mechanism of vascular necrosis of the femoral head. Qi et al. (2013) reported that triglyceride, peroxisome proliferation-activated receptor gamma, and adipocyte protein 2 levels, which are factors related to adipogenic cell proliferation/differentiation, decreased after ES-Wh treatment, although another study (Zhong and Qi, 2013) found no significant effects (Table 2).

The results of the remaining five studies are as follows, with only one paper pertaining to each of the disease groups. One animal study on the musculoskeletal system or connective tissue diseases showed that ES-Wh increased bone formation and expression bone growth-related factors in a mandibular distraction model (Peng and Yang, 2013). One animal study on endocrine, nutritional, and metabolic diseases reported that the expression of metabolism-related factors increased after ES-Wh treatment in a hyperlipidemia model (Wang et al., 1991). One animal study was based on the traditional medicine system with independent diagnostic conditions (supplementary chapter on traditional medicine conditions in the ICD-11). In this study, ES-Wh caused an increase in red blood cell-complement receptor 1, leading to a decrease in anti-cardiolipin antibody-immunoglobulin G and anti-cardiolipin antibody - immunoglobulin A levels in a “Yin-deficiency Huo-excess with chronic blood stasis model” induced by dexamethasone and adrenalin. This study reported both the preventive and therapeutic effects of ES-Wh (Yang et al., 2005). One animal study was conducted on digestive system diseases, although no significant results were reported (Xie et al., 2001) (Table 1). In a cellular study on genitourinary system diseases, ES-Wh reportedly showed preventive and therapeutic effects against autosomal dominant polycystic kidney disease by decreasing the epidermal growth factor level, a factor related to cell proliferation and differentiation (Xu et al., 2002) (Table 2).

3.4.3. ES-derived compounds and its related mechanisms in animal and cell studies

A total of 15 studies (10 animal studies, four cell studies, and one cell and animal study) evaluated ES-Cp. Depending on the type of compound, ES-Cp can be classified into a peptide series (n = 4) (Liu et al., 2012; Shan et al., 2020; Tang et al., 2010; Wang, 2020), four fibrinolytic protein types (n = 4) (Cao et al., 2011; Han et al., 2009, 2011; Yang et al., 2011), and alkaloids (n = 2) (Nong et al., 1989; Yang et al., 1989). In addition, previous studies have used polysaccharides (Xie et al., 2020), a designed anticancer protein (Wang et al., 2013), hot water extract fraction (Ni et al., 2016), isocoumarins (Jiang et al., 2012), neolignans, and norlignans (Zhu et al., 2021) (n = 1, each) (Table 3).

As with ES-Wh, the most studied disease in ES-Cp was neoplasms (n = 7). Seven studies evaluated ES-Cp in neoplasms, including liver cancer (Cao et al., 2011; Han et al., 2009, 2011; Xie et al., 2020), lung cancer (Wang et al., 2013), and other cancer cell lines (Jiang et al., 2012; Zhu et al., 2021). All of these studies reported antitumor effects of ES-Cp *in vivo* or *in vitro* by increasing antibody or lymphocyte immune activity.

The second most studied disease was circulatory system diseases (n = 3). Three studies reported vasodilation and decreased blood pressure (Nong et al., 1989), delayed electrocardiography loss and heart ischemia from carotid artery ligation (Yang et al., 1989), and anti-thrombosis

Table 1
Characteristics of the included animal studies on extracted or dried whole *Eupolyphaga sinensis* Walker.

Author (Year)	Animal	Target disease (Disease model)	Eupolyphaga administration			Effects of Eupolyphaga
			Preparation method	Dose (Period, Route)	Time (Pre/Post/Concurrently)	
Neoplasms						
Zhan et al. (2016)	Mouse (Balb/c)	Breast cancer (Xenotransplantation)	70% EtOH	200, 400 mg/kg (14 d, i.g)	Post	1) Tumor weight: ↓ 2) Colony formation of breast cancer cells: ↓
Dai et al. (2014b)	Mouse (Kunming)	Chronic myeloid leukemia (Xenotransplantation)	70% EtOH	100, 200, 400 mg/kg (10 d, i.g)	Post	1) Tumor weight: ↓ 2) Spleen weight, body weight: ↑
Zhang et al. (2014)	Mouse (Balb/c)	Hepatocellular carcinoma (Xenotransplantation)	70% EtOH	400 mg/kg (10 d, i.g)	Post	1) Tumor weight: ↓
Ge et al. (2012)	Mouse (ICR)	Hepatocarcinoma (Xenotransplantation)	95% EtOH	31, 62, 124 g/kg (14 d, i.g)	Post	1) Immune regulation (Th1 type cytokines): IFN-γ, TNF-α↑ 2) Cell proliferation, differentiation: G0, G1↑, S↓ 3) Cell death: apoptosis↑, caspase-3↑, Bax↑, Bcl-2↓, Bax/Bcl-2↑ 4) Tumor weight: ↓ 5) ALT: ↑* 6) Spleen weight/body weight: ↑
Endocrine, nutritional or metabolic diseases						
Wang et al. (1991)	Quail	Hyperlipidemia (High fat diet)	Hot water	2.4 g/kg (60 d, i.g)	Concurrently	1) Metabolism: HDL-C/TC↑, HDL3-C↑, LCAT↑
Diseases of the immune system						
Liu et al. (2019)	Mouse (ICR)	Immune deficiency (CTX 70 mg/kg, i.p.)	Freeze-drying	0.5, 1, 2 g/kg (14 d, i.g)	Concurrently	1) Increase spleen index and thymus index: ↑ 2) Immune regulation: (NK cell↑, T cell [CD3+↑, CD4+↑, CD4+/CD8+↑], Ear swelling rate [DTH]↑), macrophages activation (carbon clearance↑, phagocytic index↑), MARKs (pJNK/JNK↓) 3) Oxidative stress: SOD↑, CAT↑, MDA↓, NO↓ 4) Inflammation: IL-2↑, TNF-α↑, IL-6↑, IL-16↑ 5) Cell death (apoptosis, necrosis): Bax/Bcl-2↓
Tang et al. (2010)	Mouse (Kunming)	Immune modulation (−)	Hot water	1.89, 3.78, 7.56 g/kg (4 w, i,g)	–	1) Immune regulation: phagocytic index↑, DTH reaction (ear thickness) ↑, O.D. value of lymphocyte proliferation induced by Con A↑, the humoral immune response assessed by antibody producing cells↑
Diseases of the musculoskeletal system or connective tissue						
Peng and Yang (2013)	Rabbit (Japanese white)	Mandibular distraction osteogenesis	Drying	2 g/ea (7 w, i,g)	Concurrently	1) New bone formation rate: ↑ 2) BMPs: ↑ (1d, 3d, 1w, 4w 7w) 3) VEGF: ↑ (1d, 3d, 1w, 4w 7w)
Diseases of the digestive system						
Xie et al. (2001)	Rat (Wistar)	Mild chronic hepatic damage (CCl4)	Hot water	0.81, 3.24 g/kg (30 d, i.g)	Post	NS
Traditional medicine conditions						
Yang et al. (2005)	Rat (Sprague Dawley)	Yin-deficiency Huo-excess with chronic blood stasis (DEX 0.5 mg/kg [13d] + ADR 0.4 mg/kg [3d], IM)	ND	5, 10 g/kg (7 or 16 d, i.g)	Pre or Post	1) Immune regulation (Preventive effect): RBC-CaR↑, RBC-CR1↑, ACA-IgG↓, ACA-IgA↓, ACA-IgM↓, D-dimmer levels (mg/L) ↓ 2) Immune regulation (Treatment effect): RBC-CaR↑, RBC-CR1↑↑, ACA-IgG↓, ACA-IgA↓, ACA-IgM↓, D-dimmer levels (mg/L) ↓ 3) Preventive effect < Treatment effect

ACA, anticardiolipin antibody; ADR, adrenaline; ALT, alanine aminotransferase; Bax, Bcl-2 associated X protein; Bcl-2, B cell lymphoma-2 protein; BMPs, bone morphogenetic proteins; CCl4, carbon tetrachloride; CAT, catalase; CD, cluster of differentiation; Con A, concanavalin A; CTX, cyclophosphamide; d. day; DEX, dexamethasone; DTH, delayed type hypersensitivity; ea, each; EtOH, ethanol; G, growth; HDL3-C, high density lipoprotein 3 cholesterol; HDL-C/TC, high-density lipoprotein cholesterol/total cholesterol; Ig, immunoglobulin; i.g, intragastric administration; IFN-γ, interferon gamma; IL, interleukin; IM; intramuscular injection, i.p, intraperitoneal injection; JNK, c-Jun N-terminal kinase; LCAT, lecithin-cholesterol acyltransferase; MAPKs, mitogen-activated protein kinases; MDA, malonyldialdehyde; ND, not described; NK, nature killer cell; NO, nitric oxide; NS, not significant; O.D, optical density; p-JNK, phosphorylated c-Jun N-terminal kinase; RBC-CaR, red blood cell cancer; RBC-CR1, red blood cell complement receptor 1; S; synthesis; SOD, superoxide dismutase; Th1, T helper type 1; TNF-α, tumor necrosis factor-α; VEGF, vascular endothelial growth factor; w, week. *increased, although still at a low level.

effects (Yang et al., 2011).

There were two studies each on the immune system diseases and endocrine, nutritional, and metabolic diseases groups. Among endocrine, nutritional, and metabolic diseases, hyperlipidemia was improved by treatment with active peptide ES, which lowered the triglyceride, total cholesterol, and low-density lipoprotein levels (Shan et al., 2020; Wang, 2020). Of the two studies dealing with immune system diseases, one reported that the ES-Cp (fraction of aqueous extracts) treatment led to interleukin (IL)-1β release in ANA-1 murine macrophages (Ni et al., 2016), while the other reported that ES-Cp (polypeptide) treatment elevated the thymus and spleen indices, enhanced macrophage phagocytic function, and increased serum IL-2 levels (Liu et al., 2012).

In a study on skin diseases, ES-Cp demonstrated antioxidant effects by controlling factors such as superoxide dismutase and catalase against ultraviolet ray-induced skin photoaging (Zhang et al., 2019).

3.5. Overview of ES-containing prescriptions studies

The 22 ES-Rx studies consisted of clinical (n = 9), animal (n = 9), and cell studies (n = 3), and one that investigated both cell and animal models. The nine clinical studies included randomized controlled trials (n = 6) and case reports (n = 3). These studies used decoctions (n = 4), capsules, pills, granules, powders, or ointments (n = 1 each) of ES. All studies prescribed oral administration, except one (Huang, 2005) which prescribed external application.

Most clinical studies (n = 4) investigated heterotopic endometriosis using decoctions containing ES, with slightly different compositions (Wu, 1993; Yi and Liu, 2018; Zhang et al., 2009a; Zhang and Wang, 2007). All four clinical studies defined heterotopic endometriosis as a disease caused by static blood and dampness turbidity. They described the role of ES as dispelling blood stasis and nodules, relieving the obstruction of collateral vessels, and treating painful conditions caused by blood stasis. In other clinical studies, ES-Rx was used as a decoction for hypertension (Wei et al., 1996), a capsule for stroke (Ghandehari et al., 2011), a tablet for rheumatoid arthritis (He et al., 2007), granules for acquired immune deficiency syndrome (Wei et al., 2006), and ointments for infertility (fallopian tube obstruction) (Huang, 2005). Among these, MLC601, an ES-Rx used for stroke, is a commercialized prescription that has been used in clinical studies on post-infarct homonymous hemianopsia and in cell and animal studies evaluating the neuroprotective and neuroproliferative effects on stroke (Ghandehari et al., 2011; Heurteaux et al., 2010).

Most cell and animal studies used various prescriptions for different diseases; thus, they seemed to be heterogeneous, except for the commonality of ES-Rx. As shown in Fig. 4, when classified by disease category, preclinical studies were conducted on cancer (colorectal and liver cancer) (Bo et al., 2007; Fang et al., 2018), liver disease (alcoholic liver disease, fibrosis, and cirrhosis of the liver) (Lin et al., 2011; Lv et al., 2007), circulatory system disease (myocardial fibrosis, myocardial ischemia, and atherosclerosis) (Shen et al., 2014; Yin et al., 2008; Zhang et al., 2009b), musculoskeletal disorders (osteonecrosis and osteoarthritis) (Ju et al., 2020; Li et al., 2009), and obesity (Wang et al., 1997). Although there were differences in the indications, among the ES-Rx listed in the classical traditional medicine, the Dahuang zhechong pill (first documented in Synopsis of Prescriptions of the Golden Chamber), a classic of traditional Chinese medicine, was applied as the only experimental study (Zhang et al., 2009b). Most studies used a modified formula by adding or subtracting ingredients from the original ES-Rx or a newly formulated prescription.

4. Discussion

This scoping review summarizes the current ES research landscape by examining the characteristics and contents of studies on ES. ES-Rx was most commonly studied (n = 22 studies), followed by ES-Cp (n = 15) and ES-Wh (n = 14). Studies on ES alone, such as ES-Cp and ES-Wh, were most common in cancer models followed by various endocrine, immune, and blood circulation diseases. In combination with other herbs, ES-Rx was most commonly evaluated in heterotopic endometriosis, followed by circulatory, genitourinary, and musculoskeletal systems diseases.

The first document in which ES was described as a medicinal insect was Shennong's Classic of Materia Medica of the Han Dynasty, and the Dahuang zhechong Pill containing ES was introduced in Zhang Zhongjing's Synopsis of Prescriptions of the Golden Chamber (Zhang et al., 2009b). As a medicinal insect (Liu et al., 2019), ES has long been used to improve blood circulation by removing blood stasis in China, Korea, and Japan (Rho and Kang, 2009; Yang et al., 2011; Zhu et al., 2021). In TEAM, blood stasis refers to a pathological condition in which blood flow slows down or stops completely (Lee et al., 2015). It is composed of extravasated blood, sluggish blood circulation, viscous blood, or congested blood, leading to pathogenic conditions. Blood stasis can cause various diseases, such as hyperviscosity, hyperlipidemia, inflammation, neoplasia, ischemic brain damage, or arteriosclerosis (Park et al., 2015). "Blood-activating and stasis-dispelling" plants (e.g., Persicae semen and *Carthami flos*) and animals (*Hirudo*, *Tabanus*, and ES) (Herbology editorial committee of Korean medicine schools, 2012; Hwang et al., 2021; Rho and Kang, 2009; Xi and Gong, 2017) are primarily used to treat this condition. Animal-based medicines are more effective at removing blood stasis than herbal plants (Ruan et al., 2012) and are being actively studied for their anticoagulant and antithrombotic effects. For example, *Hirudo* is effective in wound repair, diabetic complications, and cerebral hemorrhage and exhibits anti-fibrosis, antitumor, and anti-hyperuricemia effects (Chen et al., 2021). However, limited studies have been conducted on ES.

Based on our results, the number of studies using ES-Wh increased rapidly after 2010 although decreased slightly after 2016. Meanwhile, studies on ES-Cp have been steadily conducted since 2010. Thus, future studies on ES should focus on particular active substances obtained by isolation and purification rather than the entire ES extract, which is the current TEAM-based herbal medicine application method. Most studies were conducted in China (90.5% of the corresponding authors were Chinese) and were written mostly in Chinese. However, there are recent studies in English.

Regarding the use of drugs based on TEAM, the form of the prepared medicine depends on the medicinal properties, therapeutic purpose, and route of administration. The most widely used form is a liquid medicine taken after removing the dregs by boiling the ingredients in water, called a decoction. Various extraction methods are used (Alamgir, 2017), and the extracted components differ based on the extraction method. Alcohol extraction from medicinal insects and animals is a common method. In ES preparation, hot water and 70% ethanol extraction methods were the most frequently used. One study reported that 70% ethanol extraction was more effective in inhibiting the proliferation of lung cancer cells than hot water extraction or 95% ethanol extraction (Dai et al., 2014a). However, no other studies compared the efficacy or mechanisms resulting from different preparation methods. For these reasons, we could not derive the difference in the ingredients or the effect according to the method of preparation. Future studies should determine the most appropriate preparation method for the treatment of various diseases.

The main mechanisms of ES in cancer, immune system-related diseases, and endocrine or metabolic diseases were investigated. ES reduces the growth of neoplasms by inhibiting cell proliferation and differentiation, mainly through cell cycle regulation or by inducing apoptosis in abnormally proliferating cells (Diaz-Moralli et al., 2013; Lowe and Lin, 2000). It also regulates the activity of proteins associated with apoptosis (Bax and B cell lymphoma-2 protein), cell differentiation and proliferation (cyclin and cyclin-dependent kinase), and tumor suppression (Wnt, transforming growth factor-β, and mammalian target of rapamycin) (Robert and Pelletier, 2009; Sartorius et al., 2019; Zhang et al., 2014). In our analysis, the mechanism by which ES inhibits cell

Table 2
Characteristics of the included cellular studies on extracted or dried whole *Eupolyphaga sinensis* Walker.

Author (Year)	Cell	Target disease (Disease model)	Eupolyphaga administration			Effects of Eupolyphaga
			Preparation method	Dose (Period)	Time (Pre/Post/ Concurrently)	
Neoplasms						
Zhan et al. (2016)	MDA-MB-435s and MDA-MB-231	Breast cancer (−)	70% EtOH	MDA-MB-435s: 0.075/0.15/0.30 mg/ml MDA-MB-231: 0.10/ 0.20/0.40 mg/ml (48h)	–	1) Tumor colony formation: ↓ 2) Cell proliferation/differentiation: ERK1/2↓, CXCR4↓ 3) Angiogenesis/migration (Invasion): VEGF↓, SDF-1α ↓, MMP2↓, MMP9↓
Dai et al. (2014b)	K562	Chronic myeloid leukemia (−)	70% EtOH	0.05/0.1/0.2 mg/ml (24–72h)	–	1) Cell proliferation (cell cycle): G2–M↑, G0–G1↓[#] cyclin B1↑, CDC2↑, cyclin D1↓, cyclin E↓, CDC25↓, p53↓ 2) Cell survival: EGF↓, EGFR↓, p-Akt↓, p-ERK1/ 2↓
Zhang et al. (2014)	SMMC-7721 BEL-7402 Hep G2	Hepatocellular carcinoma (−)	70% EtOH	0.05/0.1/0.2 mg/ml (48h)	–	1) Cell proliferation (cell cycle): inhibitory rate↑, colony formation↓, G0–G1↑, Cyclin D1↑, Cyclin E↓, Cyclin B↓, CDC2↓ 2) Cell survival: PKCβ↓, Akt↓, p-Akt↓, m-TOR↓, p-m-TOR↓, ERK1/2↓, MEK-2↓, Raf↓ 3) Cell migration: PKCβ↓, MMP2↓, MMP9↓, CXCR4↓, PLG↓, NFkB↓, P53↓
Dai et al. (2014a)	A549, HUVECs	Lung cancer (−)	70% EtOH	0.075/0.15/0.30 mg/ml (48h, wound healing assay 24, 48, 72h)	Post (wound healing assay)	1) Cell growth inhibition rate: 70% EtOH >95% EtOH, Hot water 2) Proliferation↓ (in endothelial cell) 3) Angiogenesis/migration: migration (wound healing assay) ↓, tube formation↓, angiogenesis (microvessel)↓, KDR signal (KDR↓, Akt↓, ERK1/2↓)
Haematopoietic system						
Qi et al. (2013)	Bone marrow mesenchymal stem cells from rat	Vascular necrosis of femoral head (DEX)	ND	1.8/3.6/7.2 g/kg	Pre	1) Adipogenic cell proliferation/ differentiation: TG (mg/L)↓, PPARγ↓, aP2 ↓
Zhong and Qi (2013)	Bone marrow mesenchymal stem cells from rat	Vascular necrosis of femoral head	ND	7.2 g/kg 2/d	Pre	NS
Diseases of the genitourinary system						
Xu et al. (2002)	Kidney epithelial cells from rat	Autosomal dominant polycystic kidney disease	Hot water	1/2.5/5% (48h)	Pre or Post	1) Cell proliferation/differentiation: EGF ↓ (pre, post)

Akt, protein kinase B; aP2, adipocyte protein 2; CDC, cell-division cycle; CXCR4, CXC chemokine receptor 4; d, day; DEX, dexamethasone; EGF, epidermal growth factor; EGFR, epidermal growth factor receptor; ERK, extracellular signal regulated kinase; EtOH, ethanol; G, growth; h, hour; HUVECs, human umbilical vein endothelial cells; KDR, kinase-insert domain containing receptor; M, mitosis; MEK, mitogen-activated protein kinase; MMP, matrix metalloproteinase; m-TOR, mammalian target of rapamycin; ND, not described; NFkB, nuclear factor kappa B; NS, Not Significant; P, protein; p-Akt, phosphorylated Akt; p-ERK, phosphorylated ERK; PKCβ, protein kinase C beta; PLG, plasminogen; p-m-TOR, phosphorylated mammalian target of rapamycin; PPAR, peroxisome proliferation-activated receptor; Raf, rapidly accelerated fibrosarcoma; SDF, stromal cell–derived factor; TG, triglyceride; VEGF, vascular endothelial growth factor; [#]:not cell death, only cell cycle arrest.

proliferation by suppressing the cell cycle, such as reducing the "S" phase population of cancer cells, was similarly explained (Ge et al., 2012; Zhang et al., 2014). In general, B cell lymphoma-2 protein regulates processes leading to the mitochondrial pathway, whereas Bax promotes apoptosis via the mitochondrial pathway. One study used ES to treat a hepatocarcinoma cell line (H22) and reported increased caspase-3 and Bax expression and Bax/B cell lymphoma-2 protein ratio due to the induction of cell apoptosis, which inhibited cancer cell proliferation. In animal experiments, ES inhibited neoplasia and reduced tumor size (Ge et al., 2012). These studies demonstrate that ES contributes to the normalization of the cell proliferation cycle by inhibiting the abnormal proliferation of neoplasia or cancer cells and inducing the apoptosis of abnormally proliferating cells.

Meanwhile, in tumor cell metastasis, which is important for patient prognosis, migration and invasion of tumor cells are key factors. These processes include cell adhesion, invasion, proliferation, and angiogenesis. Factors related to tumor cell proliferation and metastasis pathways are related to the following pathways: phosphatidylinositol 3-kinase/ protein kinase B, Ras/Raf/mitogen-activated protein kinase, phospholipase-Cγ/protein kinase C, cyclins, cyclin-dependent kinases, matrix metalloproteinases (MMPs), and endogenous CXC chemokine receptor-4 (Zhang et al., 2014). ES inhibited (1) cell migration by inhibiting protein kinase C beta, MMP2, MMP9, CXC chemokine receptor-4, plasminogen, nuclear factor kappa B, and P53 (Zhang et al., 2014), and (2) invasion by suppressing vascular endothelial growth factor, stromal cell-derived factor-1α, MMP2, and MMP9 (Zhan et al., 2016). In addition, ES inhibited cell survival by decreasing the levels of epidermal growth factor, epidermal growth factor receptor, phosphorylated protein kinase B, and phosphorylated extracellular signal-regulated kinase1/2 (Dai et al., 2014a; Zhang et al., 2014). These findings show that ES suppresses the MMP2 and MMP9 pathways and the expression of the kinase-insert domain-containing receptor, protein kinase B, and extracellular signal-regulated kinase 1/2, which are kinase-insert domain-containing receptor signals, thereby inhibiting the proliferation and metastasis of tumor cells.

Immunity refers to responding to microorganisms introduced from outside the body or by-products created by microorganisms and is an important factor in maintaining human health and healing diseases. In particular, various cytokines play key roles in the immune system. The increased production of T helper type 1 cytokines due to factors, such as IL-2, promotes T lymphocyte production and induces natural killer cell differentiation (Belardelli, 1995; Tomar et al., 2018). This immune reaction improves the body's defense system by neutralizing pathogens outside the human body (Hawkins, 2018). Our review showed that ES

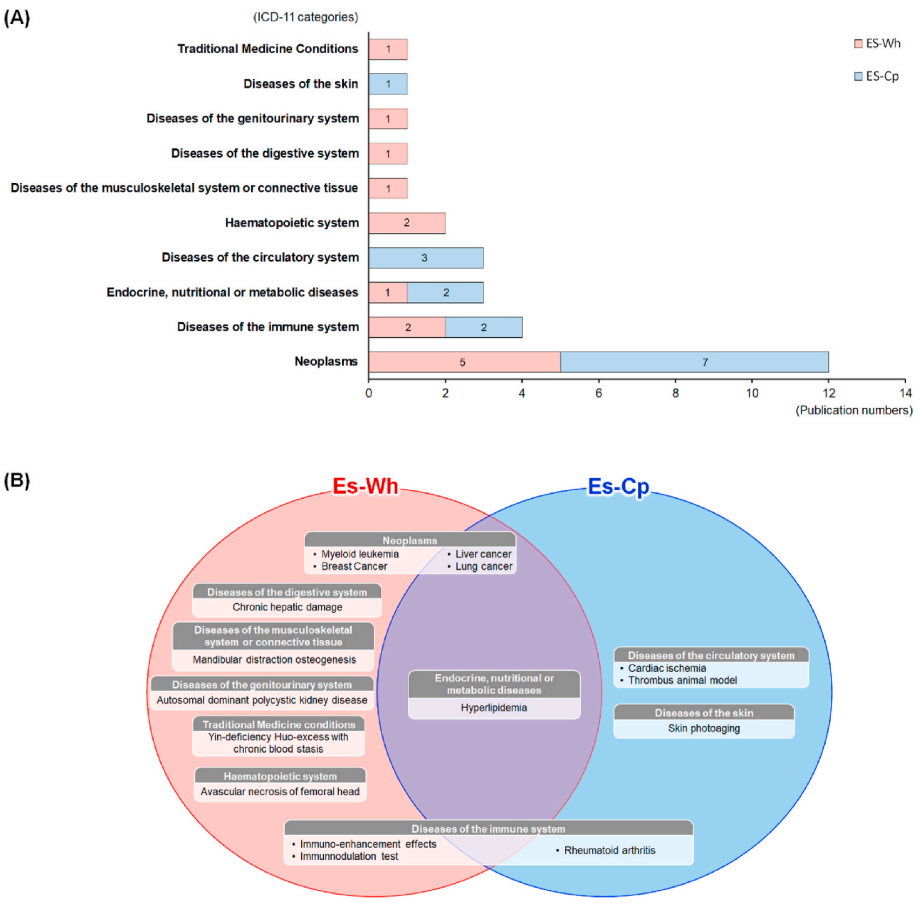

Fig. 3. Disease distribution **(A)** and Venn diagram **(B)** of ES-Wh and ES-Cp studies based on the International Classification of Diseases 11th Revision categories. ES: *Eupolyphaga sinensis* Walker; ES-Wh: extracted or dried whole ES; ES-Cp: ES-derived compounds.

improved innate immune function by promoting natural killer cell differentiation and increasing the expression of $CD3^+$, $CD4^+$, and $CD4^+/CD8^+$ T cells (Liu et al., 2019). In addition, it is involved in immune regulation by increasing carbon clearance and phagocytic index by regulating macrophage activation, one of the most representative immune cells. Immune function is also closely associated with antioxidant-related factors and inflammatory regulators (Pratheeshkumar and Kuttan, 2011). Oxidative stress is mainly related to factors such as superoxide dismutase, catalase, and nitric oxide (Vida et al., 2014), which cause cell damage and aging, thereby affecting the occurrence and progression of various diseases, such as pain, degenerative brain disease, and cancer. ES induced antioxidant effects by activating superoxide dismutase and catalase and inhibiting malonyldialdehyde and nitric oxide. In addition, the expression of inflammatory regulators, such as IL-2, tumor necrosis factor-alpha, IL-6, and IL-16, increased after ES treatment in an immune-suppressed state (Liu et al., 2019). ES can also activate T helper type 1-type cytokines, such as tumor necrosis factor-alpha and interferon-gamma (Ge et al., 2012). Thus, ES effectively increases immune function through regulation of innate immune-related cells and the antioxidant system.

Endocrine and metabolic diseases are widespread. There are various hormonal system disorders, such as abnormalities in the hypothalamus-pituitary-adrenal axis or hypothalamus-pituitary-ovary axis, hyperlipidemia, and diabetes. ES-Wh activates metabolism by increasing high-density lipoprotein cholesterol/total cholesterol, high-density lipoprotein 3 cholesterol, and lecithin-cholesterol acyltransferase levels (Wang, 2020). Peptides, a type of ES-Cp, can lower triglyceride, total cholesterol, and low-density lipoprotein levels (Shan et al., 2020; Wang, 2020). Many studies have used ES-Rx to treat hyperlipidemia (Wang et al., 1997) or heterotopic endometriosis in genitourinary system diseases (Yi and Liu, 2018; Zhang et al., 2009a; Zhang and Wang, 2007). However, a study on heterotopic endometriosis only presented the clinical effects and did not suggest a mechanism of action; therefore, more detailed modes of action should be investigated. Future studies should also focus on the hypothalamus–pituitary–adrenal or hypothalamus–pituitary–ovary axes.

As per classical literature, the medical efficacy of ES is mainly through the "removal of static blood," an important concept in TEAM, as it is a cause of various diseases and is itself a pathological condition. Fig. 4 presents the different ES-Rxs described in classical literature and the corresponding treatment indications. Diseases such as hemorrhoids and contusion, childbirth, and the puerperium appear unrelated in modern medicine. However, according to TEAM, they are all caused by "static blood," related to excessive blood or poor circulation. However, the ES-Rx studies in this review (outer part of Fig. 4, pale yellow portion) were conducted for broader disease categories compared with those in classical literature (inner part of Fig. 4). According to Park et al. (2015), the complex meaning of "static blood" was divided into four types: "disorder of blood circulation," "extravasated blood," "foul blood," and "blood congested in viscera and tissue." Related diseases and treatment drugs are also diverse. Various diseases and disease categories were treated with ES in this review; however, a common denominator of these diseases is that they are caused by "static blood" or are a disease in which clinical improvement can be observed following the resolution of "static blood".

This scoping review systematically evaluated the state of current research and assessed diseases treated with ES. Our study can be used as basic evidence for future studies on medicinal insects. ES-Wh and ES-Cp studies may confirm the therapeutic efficacy and underlying mechanisms of ES-Wh and its components. However, the applicable diseases

Table 3
Characteristics of the included studies on compounds derived from *Eupolyphaga sinensis* Walker.

Author (Year)	Compound	ICD-11	Target disease (Disease model)	Animal/Cell experiment
Peptides				
Wang et al. (2020)	Active peptide	Endocrine, nutritional, or metabolic diseases	Hyperlipidemia (high-fat diet)	Animal (Sprague-Dawley rats)
Shan et al. (2020)	Active peptide DP17	Endocrine, nutritional, or metabolic diseases	Hyperlipidemia (high-fat diet)	Animal (Sprague-Dawley rats)
Zhang et al. (2019)	Polypeptides	Diseases of the skin	Skin photoaging (UV radiation-induced)	Animal (specific pathogen free mice)
Liu et al. (2012)	Polypeptide	Diseases of the immune system	Immune function (−)	Animal (Kunming mice)
Fibrinolytic proteins				
Cao et al. (2011)	Fibrinolytic protein	Neoplasms	Anti-angiogenesis (VEGF)/microvessel density (Xenotransplantation)	Animal (Kunming mice) + Cell (S180, H22)
Han et al. (2011)	Fibrinolytic protein	Neoplasms	Liver cancer (Xenotransplantation)	Animal (Kunming mice) + Cell (S180, H22)
Han et al. (2009)	Fibrinolytic protein	Neoplasms	Liver cancer (Xenotransplantation)	Animal (Kunming mice) + Cell (S180, H22)
Yang et al. (2011)	Eupolytin 1 (fibrin [ogen] olytic protein)	Diseases of the circulatory system	Anti-thrombosis (arteriovenous shunt thrombosis model)	Animal (Wistar rats) Cell (Health human whole blood)
Alkaloids				
Yang et al. (1989)	Total alkaloid	Diseases of the circulatory system	Heart ischemia (carotid ligation model)	Animal (Kunming mice, Wistar rats)
Nong et al. (1989)	Total alkaloid	Diseases of the circulatory system	Cardiac pump function by ECG (−)	Animal (Rabbits)
Etc.				
Xie et al. (2020)	Polysaccharide	Neoplasms	Cancer (Xenotransplantation) (cell line: pancreatic/breast/hepatocellur/colon/melanoma/gastric/pancreatic ductal epithelioid/keratinocytes/NK)	Animal (H22-bearing mice) Cell (Panc-1/MDA-MB-231, H22, L-02/HepG2/HCT116/B16F10/GES-1/HPDE/HaCat/NK-92)
Jiang et al. (2012)	New isocoumarins, new alkaloid, N-acetyldopamine dimer	Neoplasms	Cancer (lymphocytic leukemia/colon/lung/breat/prostate/ovarian/glioma/melanoma/pancreas)	Cell (L1210/Colon 38, HCT-116/H-125/MCF-7/LNCaP/OVC-5/U251N/MDA/PANC-1)
Wang et al. (2013)	72-kDa anticancer protein	Neoplasms	Cancer (human lung cancer)	Cell (A549)
Zhu et al. (2021)	Neolignans and Norlignans	Neoplasms	TGF-β1–induced activation of the marker genes in rat kidney cell line, human cancer cells	Cell (NRK-52e/K562, A549, Huh7)
Ni et al. (2016)	Fraction of aqueous extracts	Diseases of the immune system	Rheumatoid arthritis (macrophage cell line)	Cell (ANA-1)

ECG, electrocardiography; ICD-11, International Classification of Diseases 11th Revision; NK, natural killer; TGF, transforming growth factor; UV, ultraviolet ray; VEGF, vascular endothelial growth factor.

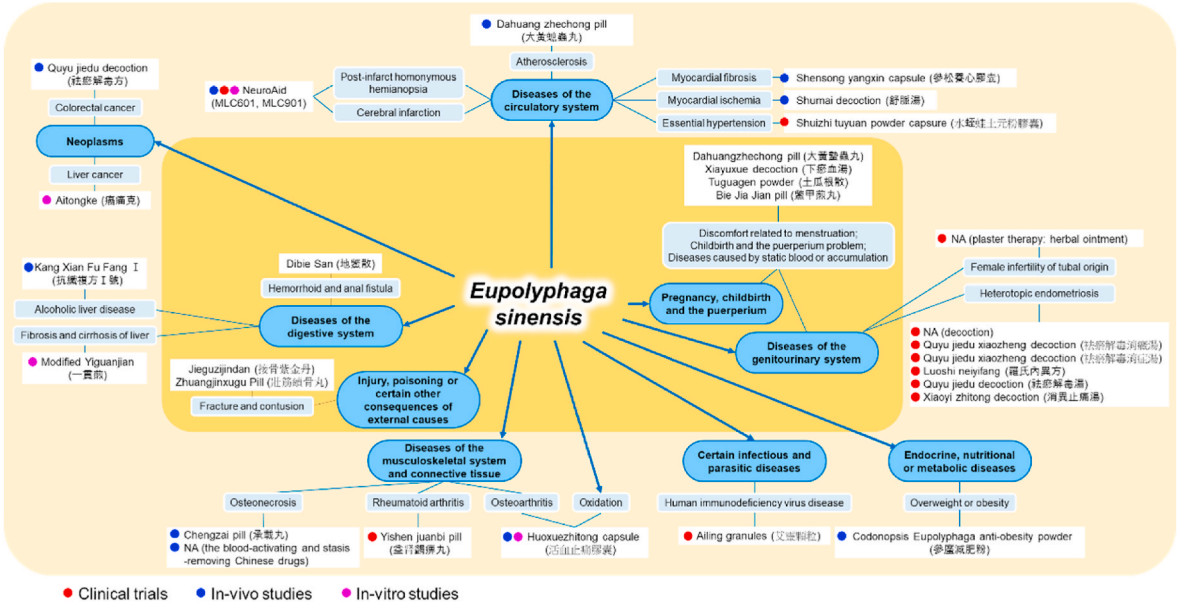

Fig. 4. Schematic diagram of disease distribution from ES-Rx studies. The inner part (dark yellow) is a simple schematic diagram of diseases and prescription names for which ES is used in the classical literature. The outer part (light yellow) represents the ES-Rx studies with broader categories than the disease category presented in the classical literature. ES: *Eupolyphaga sinensis* Walker; ES-Rx: ES-containing prescriptions; NA: not available (prescription name).

and therapeutic mechanisms of ES-Wh and ES-Cp were not completely consistent with those of ES-Rx. Because ES-Rx contains various medicinal ingredients including ES, the range of disease application may be more diverse. Nevertheless, the clinical value of ES can be confirmed by comparatively analyzing the diseases treated with ES-Rx and those treated with ES-Cp or ES-Wh.

Current studies are exploring the application of ES in many different disease models, which is advantageous in terms of high expandability of ES. The clinical application of ES for gynecological diseases such as heterotopic endometriosis, for which it has been traditionally used, is possible. ES is also believed to be beneficial for the treatment of cancers, as seen in this study. Based on the experimental data, ES appears to be involved in cell arrest and apoptosis, and it is recognized that it may be applied to various diseases related to "static blood" traditionally understood by TEAM. However, clear evidence for the specific benefits of ES for certain diseases is lacking. In order to refine ES as a universally applicable treatment intervention, some prerequisites are necessary. There is a need to classify and standardize the heterogeneity of ES, including extraction methods and dosage forms of ES as well as prescriptions in which ES is used. Information on which form of ES is more appropriate for individual patients may be beneficial for the treatment of diseases such as cancer, in which drug responsiveness often depends on genetic factors. In addition, the mechanisms of ES should be studied to determine whether more disease-specific applications can be derived from ES. For example, if changes in the hypothalamic-pituitary-ovarian axis and related hormones were also reported for gynecological diseases such as heterotopic endometriosis, where most ES-Rx studies were performed, the clinical application could be further expanded.

The research framework of complementary and alternative medicine, including herbal medicine, is distinct from general drug clinical trials in that it is scientifically evaluated "after" having treated many patients (Fønnebø et al., 2007). The patients receive the "complex including ES ″ in actual clinical situations rather than a "single ES herbal medicine." A reverse research framework that confirms the component efficacy or biological mechanisms of ES for more recent diseases based on the rationale of the classical literature will narrow the gap between basic and clinical research in the future.

5. Conclusions

This scoping review summarizes the recent experimental studies on ES-Wh, ES-Cp, and ES-Rx. These studies mainly focused on cancer and endocrine function and immunity-related diseases. We confirmed that ES exhibits therapeutic effects by regulating the cell cycle, tumor suppressor genes and proteins, immune-related biomarkers, and antioxidant molecules. Most studies on ES-Rx were clinical studies, providing insights into how ES can be used in clinical practice. This paper provides scientific evidence for the potential of ES as a medicinal insect for the treatment of various diseases. Mechanistic studies based on these therapeutic effects in clinical settings should be conducted in the future.

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CRediT authorship contribution statement

Byoung-Soo Kim: Conceptualization, Methodology, Investigation, Formal analysis, Data curation, Resources, Writing – original draft, Writing – review & editing. **Shihui Jin:** Investigation, Data curation. **Ji-Yeun Park:** Conceptualization, Methodology, Formal analysis, Data curation, Writing – original draft, Writing – review & editing, Visualization, Supervision. **Song-Yi Kim:** Methodology, Formal analysis, Data curation, Writing – original draft, Writing – review & editing, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Glossary

Bax	Bcl-2 associated X protein
Bcl-2	B cell lymphoma-2 protein
ES	*Eupolyphaga sinensis* Walker
ES-Cp	ES-derived compounds
ES-Wh	Extracted or dried whole ES
ES-Rx	ES-containing prescriptions
ICD-11	International Classification of Diseases 11th Revision
IL	interleukin
MMP	metalloproteinase
TEAM	Traditional East Asian medicine

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jep.2022.115454.

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