The efficacy, effectiveness, and safety of Kyung-ok-ko
A narrative review

Ji-Woo Kim, MSa, Ji-Hye Geum, KMDa,b,c, Won-Bae Ha, KMD, PhDabc, Hyeon-Jun Woo, KMDa,b,c, Yun-Hee Han, KMDa,c, Shin-Hyeok Park, KMDa,b,c, Jung-Han Lee, KMD, PhDabcde*.

Abstract
Kyung-ok-ko (KOK), a traditional medicinal formula in East Asia, has been recently studied across various fields. However, comprehensive reviews of clinical applications of KOK targeting clinical and experimental studies are lacking. Therefore, the application of KOK is being limited to the range of tonic medicines. To overcome this limitation, we aim to investigate the effectiveness, mechanism, and safety of KOK to obtain evidence regarding its effects in clinical applications. We searched for clinical and experimental articles in 11 databases (PubMed, Cochrane Library, Excerpta Medica database, China National Knowledge Infrastructure, Google Scholar, Research Information Sharing Service, Oriental Medicine Advanced Searching Integrated System, Korean Studies Information Service System, Korean Medical Database, DBpia, and ScienceON). We selected 54 studies based on the inclusion criteria. Three clinical studies used KOK for a consumptive disease and health promotion. Fifty-one experimental studies reported the antioxidant activity, neuroprotective activity, anticancer effect, anti-inflammatory activity, immunological activity, growth promotion, impacts on cardiovascular system diseases, gastrointestinal system diseases, respiratory system diseases, and metabolic bone disease, hepatoprotective function, and antifatigue function of KOK, which were considered effective and safe in consumptive, chronic, metabolic, inflammatory, and immune diseases. We identified the effectiveness of KOK in the treatment of a wide range of diseases. However, further clinical studies are warranted in the future.

Abbreviations: AChE = acetylcholinesterase, ALT = alanine aminotransferase, AST = aspartate aminotransferase, CD8+ = cluster of differentiation 8, GOT = glutamic oxaloacetic transaminase, GPT = glutamic pyruvate transaminase, GSH-px = glutathione peroxidase, Ig = immunoglobulin, IGF = Insulin-like growth factor, IL = interleukin, INOS = inducible nitric oxide, KOK = kyung-ok-ko, LDH = lactic dehydrogenase, MDA = malondialdehyde, MTX = methotrexate, NF-kB = nuclear factor-kappa B signaling, NO = nitric oxide, ROS = reactive oxygen species, SOD = superoxide dismutase, Th = T helper cells, TNF = tumor necrosis factor.

Keywords: herbal medicine, herb-drug interactions, Korean traditional medicine, Kyung-ok-ko, narrative review

1. Introduction

Kyung-ok-ko (KOK), which consists of Rehmannia glutinosa var. purpurea, Panax ginseng, Poria cocos, and Mel, is a traditional medicinal formula in East Asia. Since its first mention in Hong-Shi-Ji-Yan-Fang (洪氏集驗方), it has been recorded in several medical books, such as Ui-hag-gang-mog (醫學綱目), Ui-hag-ib-mun (醫學入門), and Dong-ui-bo-gam (東醫寶鑑). According to a general analysis of medical books, KOK improves health by filling jing (精) and bone marrow, treats dizziness and forgetfulness owing to the lack of brain water, and can be used for a prolonged time in gastrointestinal and respiratory diseases.[2,3]

Recent reports have demonstrated the biochemical analysis of KOK and individual herbs consisting of KOK,[4–10] and several experimental and clinical studies related to KOK have been regularly published. In addition, researchers are developing numerous products that use KOK for non-therapeutic purposes, such as food (vinegar,[11] beverages,[12] and yoghurt[13]) and cosmetics.[14]; moreover, studies have demonstrated the effectiveness of these products. Therefore, studies are being actively conducted in various fields. However, it is difficult to...
identify a comprehensive review of the clinical effectiveness of KOK in various diseases, which can be the basis for its use in the clinical field. Furthermore, despite its effects, limited KOK is being used in clinical fields, principally in the range of tonic medicines that improve health.[13] Therefore, we aimed to review clinical and experimental studies related to KOK and analyze their trends and results to address this limitation. In other words, we aimed to present sufficient evidence for the use of KOK in various clinical fields and to suggest directions for future research.

2. Methods

2.1. Search strategy

This narrative review was designed and performed in 2022 to identify articles on KOK. We used the following 11 databases: PubMed, Cochrane Library, Excerpta Medica database, China National Knowledge Infrastructure, Google Scholar for other countries, and 6 Korean databases (Research Information Sharing Service, Oriental Medicine Advanced Searching Integrated System, Koreanstudies Information Service System, Korean Medical Database, DBpia, and ScienceON). Table 1 presents the search terms for each database.

2.2. Eligibility criteria

The search was conducted from April 12, 2022 to April 19, 2022, and was limited to studies published until December 31, 2021. First, we excluded theses and dissertations from the search. Other specific inclusion and exclusion criteria for the selection of studies were set as follows.

2.2.1. Inclusion criteria.

(1) Experimental studies (in vitro, in vivo, and ex vivo studies).
(2) All clinical studies targeting humans without limiting the patient’s age, sex, period, and study design.
(3) Studies published in Korean, English, and Chinese.

2.2.2. Exclusion criteria.

(1) Studies not published in journals.
(2) Studies with unavailable original text.
(3) Literature review.

2.3. Data collection and extraction

A flowchart of the study selection process is shown in Figure 1. First, we conducted a search based on the search strategy and identified 420 articles. Screening was conducted according to the selection criteria based on 142 studies, following the removal of articles not published in Korean, English, or Chinese and duplicates. The first screening was conducted using the title and abstract, whereas the second screening involved reviewing the original text. Two authors (Ji-Woo Kim and Ji-Hye Geum) reviewed the literature independently. They discussed differences in the process and results of the literature evaluation or adjusted their opinions through discussion with a third author (Jung-Han Lee).

3. Results

3.1. The selection of target research

A total of 54 studies were eventually selected, which comprised 3 clinical studies and 51 experimental studies.

3.2. Clinical study review

For the selected clinical studies, we analyzed the results of the study design, disease, composition, and administration methods (Table 2).

3.2.1. Study design analysis. The clinical studies consisted of 2 randomized controlled trials[15,16] and 1 case report.[17]

3.2.2. An analysis of the KOK composition and medication method. Two studies used the original composition of KOK,[15,16] whereas 1 study administered KOK by adding Liriope platyphylla, Asparagus cochinchinensis, and Lycium chinense.[17]

| Table 1 |
| --- |
| Electric database and search terms used for this study. |
| **Electric databases** | **Domain** | **Search terms** |
| RISS | http://www.riiss.kr | 경옥고 |
| OASIS | http://oasis.kiom.re.kr | 경옥고 |
| KISS | https://kiss.kstudy.com | 경옥고 |
| KMbase | https://kmbase.medic.or.kr | 경옥고 |
| DBpia | https://www.dbpia.co.kr | 경옥고 |
| ScienceON | https://scienceon.kisti.re.kr | 경옥고 |
| PubMed | https://pubmed.ncbi.nlm.nih.gov | 경옥고 |
| Cochrane Library | https://www.cochranelibrary.com | 경옥고 |
| EMBASE | https://www.embase.com | 경옥고 |
| CNKI | https://www.cnki.net | 경옥고 |
| Google Scholar | https://scholar.google.co.kr | 경옥고 |

경옥고 = Korean word of Kyung-ok-ko.
Figure 1. PRISMA flow chart for the database search in this study. KOK = Kyung-ok-ko, PRISMA = Preferred Reporting Items of Systematic Reviews and Meta- Analyses.

### Table 2
Main data of clinical studies.

| References | Study design | Sample size | Conditions | Other treatment | Composition of KOK | Main outcome |
|------------|--------------|-------------|------------|-----------------|-------------------|--------------|
| Yin et al[15] | RCT | 60 (30/group) | Tuberculosis (Pulmonary-Yin-deficiency) | W-med | * | 1) Effective rate: CG 80.00%, e.g. 93.33% 2) Th1↑, Th2↓ |
| Kim et al[16] | RCT | 24 (12/group) | Normal soccer player | - | * | 1) Aerobic exercise capacity: IMP 2) Fatigue recovery: IMP |
| Wang[17] | Case report | 16 | Weakness from long-term illness (qi-deficiency) | - | *, LR, AR, LRC | 1) Symptoms: IMP 2) Infection resistance: IMP (prevalence rate↓) 3) No side effect |

* = Original composition of KOK, - = not reported, AR = Asparagi radix, CG = control group, EG = experimental group, IMP = improved, KOK = Kyung-ok-ko, LR = Liriopes radix, LRC = Lycii radicis cortex, RCT = randomized controlled trial, Th = T helper cell, W-med = Western medicine.
Table 3
Main data of experimental studies. The name of medicinal herbs was written in Latin including used parts.

| References | Study design | Composition of KOK | Activity/main mechanism |
|------------|--------------|--------------------|-------------------------|
| Xue and Au [38] | In vivo | * | Delay aging/antioxidant |
| Kwak et al [39] | In vivo | * | Delay aging/antioxidant |
| Xue and Liu [40] | In vivo | * | Improvement of the central nervous system/antioxidant of hypothalamus and delay brain neuronal disturbance |
| Qian and Wei [41] | In vivo | * | Anti-aging skin/antioxidant and hydroxylamine, hyaluronic acid, vascular endothelial growth factor, and basic fibroblast growth factor↑ |
| Qu et al [42] | In vivo | * | Delay aging/antioxidant and anti-inflammatory |
| Liu et al [43] | In vivo | * | Delay aging/antioxidant |
| Hwang et al [44] | In vivo | *, LF, ARL, ss | Inflammation of atopic dermatitis/antioxidant and anti-inflammatory |
| Jo and Cho [45] | In vitro | - | Antidepressive/anti-inflammatory and antioxidant |
| Liu et al [46] | In vitro and in vivo | RR, P, KRPG, M | Inhibited particulate matter-induced vascular barrier disruptive responses/antioxidant and anti-inflammatory |
| Lee and Bae [47] | In vitro and in vivo | *, LF, ARL, ss | Mitigate neurotoxicity and anti-blood-brain-barrier disruption/antioxidant and anti-inflammatory |
| Cho et al [48] | In vivo | * | Neuroprotective and attenuation of memory impairment/anti-inflammatory |
| Liu et al [49] | In vivo | * | Memory ameliorating/inhibit acetylcholinesterase activity |
| Chen et al [50] | In vivo | * | Learning ability and memory improvement |
| Lee et al [51] | In vivo | 1) * | Amelioration and prevention of cognitive deficits and depression among menopausal symptoms/mature brain-derived neurotrophic factor (BDNF)↑ |
| Whang et al [52] | In vivo | * | Anti-hyperlipidemia, antihypertension, antifatigue, and weight loss/cholesterol and high density lipoprotein-cholesterol↓, triglyceride↑, and the phosphorylation of phospholipase C gamma and protein kinase B↑ |
| Chen et al [53] | In vivo | 2) RR, P, Gr, AGR, Gr, Hh, OCR, LgR, Sr, Wg | Protection against cisplatin-induced kidney damage and tumor cell growth ↓ |
| Liu et al [54] | In vivo | 1) *, SM, CF, AtR, CS, HF | Inhibiting protein kinase B↓ and reducing platinum accumulation in the kidney |
| Cho et al [55] | In vivo, CH, MO, CR, CP | * | Improving learning ability and memory improvement |
| Whang et al [56] | In vivo | * | Delay aging/antioxidant |
| Kwak et al [57] | In vivo | 1) * | Anti-hyperlipidemia/total cholesterol and triglyceride↓, and the phosphorylation of phospholipase C gamma and protein kinase B↑ |
| Cha et al [58] | In vivo | * | Anti-hyperlipidemia/total cholesterol and triglyceride↓ |
| Han et al [59] | In vivo | * | Lipoprotein-cholesterol↓ |
| Jung et al [60] | In vivo | *, CH, MO, CR, CP | Anti-hyperlipidemia/total cholesterol and triglyceride↓ |
| Kim et al [61] | Ex and in vivo | *, LF, ARL, ss | Lipoprotein-cholesterol↓ |
| Kim and Song [62] | In vivo | 1) | Lipoprotein-cholesterol↓ |
| Whang et al [63] | In vivo | 2) *, SM | Lipoprotein-cholesterol↓ |
| Chen et al [64] | In vivo | * | Anti-hyperlipidemia/total cholesterol and triglyceride↓ |
| Cho et al [65] | In vivo | 3) *, SM, DF, AHR, CS, HF | Lipoprotein-cholesterol↓ |

(Continued)
### 3.3.1. Study design analysis

Of the 51 experimental studies, 35, 6, 9, and 1 were in vivo, in vitro, in vivo and ex vivo, and in vivo studies, respectively. All in vivo studies used mice as the test subjects, whereas *Drosophila melanogaster* was used as a test subject in the study by Xue et al. [14].

### 3.3.2. The composition of KOK

Of all the experimental studies, 33 studies used the original formulation composed of *Rehmannia glutinosa* var. *purpurea*, *Panax ginseng*, *Poria cocos*, and *Mel*, whereas 18 studies added other herbs to the original formulation. *Lycium chinense* and *Aquilaria agallocha* were the most commonly added and were mentioned in 8 studies. Three studies used red ginseng instead of *Panax ginseng*, and 2 studies each added *Ceratocellulon nippon*, *Lemnata edodes*, and *Cordyceps sinensis* as test subjects, whereas *Poria* and *Polygton multiform* were used as test subjects, whereas *Drosophila melanogaster* was used as a test subject in the study by Xue et al. [14].

### 3.3.3. Result analysis

The antioxidative activity analyzed in the 11 experimental studies demonstrated the most significant effect. In addition, the central nervous system and cancer had 10 reported studies each. Moreover, the studies reported on anti-inflammatory, immunological, growth-related, cardiovascular, gastrointestinal, respiratory, metabolic bone disease, hepatoprotective, and anti-fatigue effects (Fig. 2).

### 3.3.3.1. Antioxidative activity

Eleven studies have demonstrated the mechanisms underlying the antioxidative activity of KOK. Superoxide dismutase [16-23] and glutathione peroxidase [16,20,22-24] showed the highest frequency of activation via antioxidative mechanisms, with 6 studies each. Three studies reported on antioxidative mechanisms through the reduction of reactive oxygen species (ROS). [21-27] Moreover, researchers have demonstrated various antioxidative mechanisms, such as the inhibition of nitric oxide (NO) and inducible NO [26] and the reduction of plasma thiobarbituric acid reactive substance [19], lipid peroxidation, [20] malondialdehyde [21] and the activation of the anti-Kelch-like ECH-associated protein-anti-nuclear factor erythroid 2-related factor2 pathway [20].

### 3.3.4. Conclusion

Based on the results of this study, KOK may have a variety of clinical applications, including the treatment of pulmonary tuberculosis, a variety of digestive, nutritional, and metabolic disorders, such as diabetes, immunological disorders, and cancer. KOK has been demonstrated to be a safe and effective treatment for a variety of conditions, and further research is needed to confirm its efficacy and safety in clinical practice.
Regarding the efficacy of KOK through antioxidant mechanisms, 6 studies reported on anti-aging efficacy,\textsuperscript{18–23} whereas the remaining studies demonstrated relief from inflammation in atopic dermatitis,\textsuperscript{25} relief from depression,\textsuperscript{26} increased sperm production,\textsuperscript{24} relief from neurotoxicity,\textsuperscript{28} and suppression of vascular barrier destruction.\textsuperscript{27}

### 3.3.3.2. Central nervous system
Researchers have performed 10 studies on KOK and the central nervous system. Specifically, relief from memory impairment\textsuperscript{29–32} displayed the highest frequency, as reported in 4 studies. In addition, it could be divided into 3, 2 each, and 1 study on anti-aging,\textsuperscript{33–35} depression improvement\textsuperscript{26,32} and recovery from nervous system damage,\textsuperscript{20,28} and neuroprotection, respectively.\textsuperscript{29}

In a detailed analysis of the studies analyzing the mechanisms which most significantly impact the central nervous system, anti-inflammatory activity\textsuperscript{28,29,35} and antioxidant activity\textsuperscript{20,26,28} were the most commonly investigated, each being evaluated in 3 studies. Furthermore, the corresponding effect was analyzed by inhibiting acetylcholinesterase,\textsuperscript{30} regulating the metabolism of acetic acid and amino acids,\textsuperscript{33} and affecting the brain target proteins.\textsuperscript{34}

### 3.3.3.3. Anticancer effect
Ten studies reported anticancer effects, of which 7 studies reported a direct anticancer effect,\textsuperscript{36–42} and 3 studies mentioned the alleviating side effects of cisplatin chemotherapy during cancer treatment.\textsuperscript{43–45} Specifically, lung cancer was reported in 8 studies,\textsuperscript{36–40,43–45} whereas pancreatic cancer\textsuperscript{41} and liver cancer\textsuperscript{42} were each reported in 1 study.

Three studies reported alleviation of the side effects of chemotherapy following lung cancer, which were associated with the suppression of bone marrow\textsuperscript{43,44} and relief from immunosuppression.\textsuperscript{44}

### 3.3.3.4. Anti-inflammatory activity
Seven studies reported the anti-inflammatory activity of KOK. Specifically, some studies have reported anti-inflammatory activity through the reduction of cytokines\textsuperscript{27} (interleukin [IL]-1,\textsuperscript{26,29,46–48} tumor necrosis factor-\(\alpha\),\textsuperscript{11,47,48} and IL-6,\textsuperscript{28,47,48}) chemokines (IL-8 and monocyte chemoattractant protein-1),\textsuperscript{47,48} cyclooxygenase-2,\textsuperscript{28,46} and inducible NO.\textsuperscript{28,47} Moreover, anti-inflammatory activity is activated through the inhibition of the nuclear factor-kappa B signaling pathway\textsuperscript{28,31} and mitogen-activated protein kinases.\textsuperscript{28}

### 3.3.3.5. Immunological study
Five studies demonstrated immune function. First, a study improved immunity by alleviating the decrease in spleen cells, T cells, B cells, and macrophages, which are the immunotoxic effects of methotrexate, while restoring Th1 and Th2 imbalance.\textsuperscript{49} Another study increased immune activity through the activation of macrophages.\textsuperscript{150} In addition, 1 study reported a beneficial effect\textsuperscript{41} on atopic dermatitis through the reduction of immunoglobulin E, whereas 2 studies suppressed polycystic ovarian syndrome through the reduction of cluster of differentiation 8 and macrophages along with anti-inflammatory activity.\textsuperscript{47,48}

### 3.3.3.6. Growth promotion
Four studies have reported growth promotion, of which 1 demonstrated hair growth and the remaining demonstrated physical growth. The expression of proteins related to hair growth factors, such as insulin-like growth factor-1 and vascular endothelial growth factor, and macrophages, which are the immunotoxic effects of methotrexate, while restoring Th1 and Th2 imbalance.\textsuperscript{49} Another study increased immune activity through the activation of macrophages.\textsuperscript{150} In addition, 1 study reported a beneficial effect\textsuperscript{41} on atopic dermatitis through the reduction of immunoglobulin E, whereas 2 studies suppressed polycystic ovarian syndrome through the reduction of cluster of differentiation 8 and macrophages along with anti-inflammatory activity.\textsuperscript{47,48}

### 3.3.3.7. Cardiovascular study
Four of the studies were related to the cardiovascular system. Specifically, they reported anti-thrombotic activity,\textsuperscript{56} anti-hyperlipidemic effects,\textsuperscript{57,58} and protection against oxidative damage to cardiomyocytes.\textsuperscript{59}

### 3.3.3.8. Gastrointestinal study
Three studies were related to the gastrointestinal system, and each study reported the significant effects of KOK on laxation,\textsuperscript{60} the protection of gastric mucosa,\textsuperscript{61} acute and chronic anti-inflammatory effects, ulcer suppression, and analgesia.\textsuperscript{62}

### 3.3.3.9. Respiratory study
Two studies were related to the respiratory system. One study reported expectorant and antitussive effects,\textsuperscript{63} whereas another demonstrated the efficacy of KOK in antituberculosis and reduced drug resistance when co-administered with antituberculosis agents.\textsuperscript{64}
3.3.3.10. **Metabolic bone disease** Two studies were related to metabolic bone diseases. One study reported on a significant effect on osteoporosis owing to estrogen deficiency, whereas another reported on the inhibition of osteoblast proliferation and bone resorption in inflammatory bone loss.

3.3.3.11. **Hepatoprotective study** One study reported the hepatoprotective effect of KOK, which demonstrated the improvement and prevention of liver damage by not only inhibiting serum glutamic oxaloacetic transaminase and glutamic pyruvate transaminase activity, but also suppressing the formation of thiobarbituric acid and improving lesions of hepatic tissues in combination with glutathione.

3.3.3.12. **Antifatigue effect** One study reported the antifatigue effect of KOK by decreasing serum lactate and increasing serum glucose and intramuscular glycogen levels.

3.3.3.13. **Toxicity and side effects of KOK** Eight studies reported the toxicity and side effects of KOK. Of them, 6 studies conducted experiments on the toxicity of KOK and predominantly demonstrated the absence of cytotoxicity. Specifically, 1 study reported that average weight, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, tumor necrosis factor-α, and Fas in the liver and kidney were unaffected by KOK administration. Also, KOK did not induce toxicity even when administered for a long time.

Three studies mentioned the side effects of KOK. Some studies reported that serum glutamic oxaloacetic transaminase and glutamic pyruvate transaminase levels did not change during KOK administration; therefore, KOK did not exert a negative effect on liver function. Regarding the anti-thrombotic effect of KOK, 1 study reported its potential advantage over aspirin in terms of side effects due to shorter bleeding time compared with aspirin.

4. **Discussion**

KOK has been described in various medical books, such as *Ui-hag-gang-mog* (醫學經目), *Ui-hag-ib-mun* (醫學入門), and *Dong-ui-bo-gam* (東醫寶鑑), since its first report in *Hong-Shi-Ji-Yan-Fang* (洪氏集雛方). Moreover, it is 1 of the most widely used prescriptions in East Asia consisting of *Rehmannia glutinosa* var. purpurea, *Panax ginseng*, *Poria cocos*, and *Med.*. It can be improved by filling Jing (精) and bone marrow or for consumable cold and Jo (煩) patterns because of body fluid deficiency. Particularly, *Ui-hag-ib-mun*, *Jingyue Quanshu* (景岳全书), and *Dong-ui-bo-gam* mentioned that 1 to 3 herbs could be added to the original composition of KOK to produce Gami-KOK with specific effects. KOK can be generally used for tonic medicine and contraceptive diseases, and can also be used for various diseases by appropriately adding or subtracting herbs. Researchers have actively investigated and reported the biochemical analysis of KOK and its individual herbs consisting of KOK in recent years. KOK contains amino acids (valine, aspartic acid, and arginine) and 14 minerals (K and Na). Particularly, the extract using chloroform as a solvent displayed highest antioxidative activity. Moreover, while examining each of the studies on the individual herbs that constitute KOK, the primary herb *Rehmannia glutinosa* var. Purpurea displays efficacy in various inflammatory and metabolic diseases owing to its anti-inflammatory, antioxidant, hypoglycemic, and autonomic nervous system activities. *Poria cocos* is composed of chemical components, such as triterpenes and polysaccharides, which effectively inhibit cytokine secretion, enhance immunity, anticancer, and gastrointestinal and renal diseases. *Panax ginseng* comprises ginsenoside as the major component, and displays antioxidant, anti-inflammatory, and immune-stimulating activities by inhibiting the production of ROS and promoting NO production. Moreover, it is effective in the cardiovascular system, neurodegenerative diseases, diabetes, and complications owing to these activities. Furthermore, numerous experimental and clinical studies have demonstrated the effects of KOK; however, it is difficult to identify comprehensive research. One review study on the efficacy of KOK based on historical medical books exists, however, it focused on medical books and analyzed only 7 Korean studies. These reasons eventually contributed to narrowing the range of KOK use in clinical fields. Currently, KOK is principally used in a limited range of tonic medicines. Therefore, we reviewed and analyzed KOK-related studies through 11 database searches to collect sufficient evidence for its clinical use and suggest directions for future research.

A total of 54 studies were related to KOK, of which 3 were clinical studies. Each study focused on pulmonary tuberculosis, a patterned deficiency of pulmonary-Yin, fatigue, and weakness following prolonged illness and patterned qi-deficiency. They reported on the useful effects of KOK as a treatment for diseases as well as a tonic medicine. In addition, 1 study by Wang used a combination of *Liriope platyphylla*, *Asparagus cochinchinensis*, and *Lycium chinense* with KOK, which were added from *Dong-uy-bo-gam*. This can form the basis for the increase in the range of KOK through the addition of the aforementioned herbs. Unlike these studies, 1 study combined KOK with Western medicine; nonetheless, a control group was treated only with identical Western medicine. Eventually, all clinical studies revealed a single effect of KOK.

We identified 51 experimental studies on KOK. In addition to the original composition of KOK, various herbs were added to it. Specifically, 33 studies used the original composition, whereas 18 studies added herbs. *Lycium chinense* and *Aquilaria agallocha* were the most commonly added herbs, and were identified in 8 studies. *Lycium chinense* inhibits malondialdehyde formation, activates the removal of superoxide anions and anti-superoxide formation, prevents or alleviates oxidative stress-induced hepatotoxicity. Furthermore, it is useful as a treatment for learning and memory deficits induced by trimethyl-lysin. *Aquilaria agallocha*, with 4-butyl-a-agaroaruran as the primary component, exerted an anxiolytic effect in an animal model. Based on the efficacy of these herbs, their combination with KOK can enhance its antioxidative activity and effect on the central nervous system.

Red ginseng was used instead of *Panax ginseng* in 3 studies, and was principally used to relieve depression, anticanter effects, and immune activity. Only 1 study used red ginseng instead of *Panax ginseng*, without the addition of other herbs, and it was reportedly effective in relieving depression. This result was consistent with that of another study demonstrating that red ginseng alleviates depression by improving the function of the astrocytic gap junction. Therefore, red ginseng can be used instead of *Panax ginseng* in the original composition upon the use of KOK in patients with depression.

In contrast, studies that added other herbs had a limitation in that it is difficult to analyze the efficacy of KOK itself. Thus, we identified studies that compared the efficacies of KOK and Gami-KOK, which suggested that some herbs were added to KOK. KOK itself was mentioned to display the expected efficacy; nonetheless, it can produce better effects upon using Gami-KOK. This finding was consistent with the mention in the *Ui-hag-ib-mun*, *Jingyue Quanshu*, and *Dong-ui-bo-gam* that Gami-KOK can be manufactured with a specific function by adding 1 to 3 herbs to KOK. Therefore, upon performing additional complementary research in the future, KOK will likely treat various diseases by adding herbs based on the symptoms of a patient in actual clinical practice.

Regarding the effects of KOK in experimental studies, 11, 10 each, 7, 5, 4, 3, 2 each, and 1 each study demonstrated significant antioxidative activity, diseases of the central nervous system and anticancer effect, anti-inflammatory activity, immune activity,
growth promotion and cardiovascular system diseases, diseases of the gastrointestinal system, respiratory system diseases and metabolic bone diseases, and hepatoprotective and antifatigue effects, respectively. The predominantly analyzed antioxidative activity, which refers to the removal of free radicals generated in the body, has attracted interest in modern medicine.[74,75] This is because oxidative stress owing to an increase in free radicals changes the oxidation-reduction state of cells and induces inflammation.[76] These harmful actions affect the liver, central nervous system, heart, and testicles, thus causing chronic diseases and metabolic disorders.[77,78] Furthermore, it can be a disabling factor for adult diseases and acute or chronic diseases.[79] KOK displayed antioxidative activity through various mechanisms, such as the activation of superoxide dismutase or glutathione peroxidase and the reduction of ROS. Based on these mechanisms, KOK exerts significant effects, such as anti-aging, recovery from damage to the central nervous system, increased reproductive capacity, and the alleviation of atopic dermatitis. In other words, KOK could be widely used in chronic, metabolic, and aging diseases in the future.

We analyzed the effects of KOK on the central nervous system and its anticancer activity. KOK affects the nervous system through antioxidant activity, anti-inflammatory activity, the inhibition of acetylcholinesterase, the regulation of acetoacetic or amino acids, and influencer activity of brain proteins. One study reported that KOK could be applied for the prevention and treatment of Alzheimer’s disease through the PI3K-Akt signaling pathway, the regulation of the actin cytoskeleton pathway, and insulin resistance pathway based on pharmaceutical analysis.[79] Particularly, 8 studies were related to memory impairment and nerves; therefore, KOK is also effective in neurodegenerative diseases. Subsequently, regarding its anticancer effect, 8 of 10 studies demonstrated the effects through the inhibition of the cell growth rate, the regulation of the cell cycle, and increased percentage of apoptosis in relation to lung cancer. Some studies have reported that KOK inhibits the toxicity of cisplatin, which is used for chemotherapy in western medicine.[80,81] Cisplatin has approximately 40 specific toxicities, including nephrotoxicity, ototoxicity, neurotoxicity, gastrointestinal toxicity, hemotologic toxicity, cardiotoxicity, and hepatotoxicity.[79] Of these, nephrotoxicity is predominant, and the overall prevalence of cisplatin-induced nephrotoxicity in clinical practice has been identified in one-third of the treated patients.[79,80] In addition, concerning the side effects of Western medicine, KOK inhibited the nephrotoxicity of cisplatin,[81] alleviated the toxicity of methotrexate,[82] decreased resistance to Mycobacterium tuberculosis when administered in combination with antibiotics,[83] and inhibited liver damage when administered in combination with glutathione.[84] A comprehensive analysis suggested that clinicians can consider the use of KOK as a herbal medicine when considering integrative medicine for patients undergoing cancer treatments, including chemotherapy with cisplatin, in clinical practice.

Additionally, KOK exerts anti-inflammatory and immune effects. The mechanism of its anti-inflammatory effect involves the reduction of cytokines and chemokines, whereas the mechanism of its immune effects involves the reduction of immunoglobulin E, cluster of differentiation 8, and macrophage expression, thereby suggesting that KOK could be applied to inflammatory and immune diseases in the future.

One clinical study and 8 experimental studies reported the toxicity and side effects of KOK. Jang et al.[85] reported no toxicity in the liver and kidneys even after relatively prolonged administration (22 days).

In summary, we analyzed 54 studies related to KOK, the majority of which were experimental studies. Its efficacies include antioxidant, anticancer, anti-inflammatory, immune, and growth-promoting activities, in addition to central nervous system, cardiovascular, gastrointestinal, and respiratory effects, without significant toxicity or side effects. However, most of these results were analyzed through experimental studies, thus necessitating additional research to determine the presence of similar effects and safety in humans. Moreover, there have been only 3 clinical studies on KOK, which was reportedly effective in improving health, except for the treatment of pulmonary tuberculosis. Therefore, our review had a limitation in that it was not possible to determine the applicability of the therapeutic effects of KOK analyzed in experimental studies on the human body. Therefore, additional research on the possibility of its clinical application is required.

5. Conclusion

KOK can be effective in various diseases through its antioxidiant, anticancer, anti-inflammatory, immune, and growth-promoting properties, in addition to the central nervous system, cardiovascular, gastrointestinal, and respiratory effects, without significant toxicity or side effects. Further clinical studies are required in the future to prove its efficacy in clinical practice.

Acknowledgements

We would like to thank Editage (www.editage.co.kr) for the English language editing.

Author contributions

Conceptualization: Ji-Woo Kim and Ji-Hye Geum.
Data curation: Ji-Woo Kim.
Investigation: Ji-Woo Kim and Ji-Hye Geum.
Methodology: Hyeon-Jun Woo, Yun-Hee Han, and Shin-Hyeok Park.
Project administration: Ji-Hye Geum.
Supervision: Won-Bae Ha and Jung-Han Lee.
Validation: Won-Bae Ha, Hyeon-Jun Woo, Yun-Hee Han, and Shin-Hyeok Park.
Visualization: Ji-Woo Kim and Ji-Hye Geum.
Writing – original draft: Ji-Woo Kim and Ji-Hye Geum.
Writing – review and editing: Ji-Hye Geum, Won-Bae Ha, Hyeon-Jun Woo, Yun-Hee Han, Shin-Hyeok Park, and Jung-Han Lee.

References

[1] Hur J. Donguibogam (原本 東醫寶鑑). new version. Seoul, Republic of Korea: Nam-san-dang; 2014:78.
[2] Kim MD. The Literature Study on the efficacy and manufacturing process of Gyeongoggo. J Korean Class. 2011;24:51–64.
[3] Lee JH, Seo YB, Kim BS. A study of modern application of Kyungohkgo through historical analysis of its virtues. J Haewha Med. 2016;24:25–34.
[4] Lee SY, Shin YJ, Park JH, Kim SM, Park CS. An analysis of the Gyungokgo's ingredients and a comparison study on anti-oxidation effects according to the kinds of extract. Kor J Herbology. 2018;23:123–36.
[5] Kim SH, Yook TH, Kim JU. Rehmanniae radix, an effective treatment for patients with various inflammatory and metabolic diseases: results from a review of Korean publications. J Pharmacopuncture. 2017;20:81–8.
[6] Rios JL. Chemical constituents and pharmacological properties of Porá cacos. Planta Med. 2011;77:681–91.
[7] Lee SM, Lee YJ, Yoon JJ, Kang DG, Lee HS. Effect of Porá cacos on hypertoncic stress-induced water channel expression and apoptosis in renal collecting duct cells. J Ethnopharmacol. 2012;141:368–76.
[8] Huyan SH, Bhihlae KD, In G, Park CK, Kim JH. Effects of panax ginseng and ginsenosides on oxidative stress and cardiovascular diseases: pharmacological and therapeutic roles. J Ginseng Res. 2022;46:33–8.
[9] Cho IH. Effects of panax ginseng in neurodegenerative diseases. J Ginseng Res. 2012;36:342–53.
[10] Lin Z, Xie R, Zhong C, Huang J, Shi P, Yao H. Recent progress (2015–2020) in the investigation of the pharmacological effects and mechanisms of ginsenoside Rbl, a main active ingredient in panax ginseng Meyer. J Ginseng Res. 2022;46:59–53.
[36] Zhang Q, Xie QL, Chen X, Sun L, Ye K, Tang C. Effect of Qiongyuogao on the action of DDP in inhibiting the division of GLC-82 cell strain in vitro. Zhong Yao Cai. 2000;23:694–6.

[37] Chen X, Shen Z. Effect of Qiongyuogao on the expression of NM23 and PCNA of experimental lung cancer mice treated by chemotherapy. J Anhui Univ Chin Med. 2000;19:47–9.

[38] Chen XY, Shen Q. Studies on effects of Qiongyuogao on cell cycle and apoptosis of GLC-82 cell strain. Chin Trad Pat Med. 2000;22:44–6.

[39] Chen XY, Wei B, Sun L, Li QM. Experimental study on the effect of Qiongyuogao on the efficacy and attenuation of chemotherapy in mice with experimental lung cancer [琼玉膏对实验性肺小鼠化疗效果的抑制和减毒作用的研究]. Shannxi J Trad Chin Med. 2003:24:376–7.

[40] Lee ES, Seo BI, Lee JU, Bae JS. Effects of Qiongyuogao and prescription of modified Qiongyuogao on lung cancer. Kor J Herbol. 2002;17:101–9.

[41] Liu L, Liu DS, Li ZD, Li JW, Wu XL. Synergistic and attenuating effects of Qiongyugao on pancreatic cancer mice with chemotherapy. Chin J Pathophysiol. 2019;35:2181–6.

[42] Chen XY, Wei CS, Tong GD, Mao HJ, Xia F, Jiang ZY. Preventive and therapeutic effects of Qiongyuogao on hepatocellular carcinoma via inhibition of the expression of HBxAg in hepatic carcinoma cells. Xi Bao Yu Fen Zi Mian Yi Xue Za Zhi. 2007;23:36–9.

[43] Chen XY, Xia F, Xu YS, Yang QH. Qiongyuogao for the bone marrow inhibition of mice with pulmonary adenocarcinoma. Chin J Clin Rehabil. 2005;9:259–61.

[44] Chen XY. The effect of Qiongyuogao on the levels of serum interleukin-2 and tumor cytokotic factor in immunosuppressed mice induced by chemotherapy in experimental lung cancer [琼玉膏对实验性肺癌小鼠化疗抑制免疫的血清细胞因子IL-2及肿瘤因子含量的影响]. Nan Ch Asia Med. 2002;34:61–2.

[45] Chen XY. Qiongyuogao alleviates the inhibition of bone marrow nucleated cell division caused by chemotherapy in mice with experimental lung cancer [琼玉膏减轻实验肺癌小鼠化疗导致骨髓有核细胞分裂的抑制]. Chin Trad Pat Med. 2005;27:121–3.

[46] Teng ZY, Cheng XL, Cai XT, et al. Ancient Chinese formula Qiong-Yu-Gao protects against cisplatin-induced nephrotoxicity without reducing anti-tumor activity. Sci Rep. 2015;5:15592.

[47] Jang M, Lee MJ, Lee JM, et al. Oriental medicine Kyung-ok-Ko prevents and alleviates dehydroepiandrosterone-induced polycystic ovarian syndrome in rats. PLoS One. 2014;9:e87623.

[48] Lee MJ, Jang M, Bae CS, et al. Effects of oriental medicine Kyung-ok-Ko on uterine abnormality in Hyperandrogenized rats. Rejuvenation Res. 2016;19:456–66.

[49] Rob SS, Lee WH, Kim KM, Na MK, Bae JS. Immune-enhancing effects of a traditional herbal prescription, Kyung-ok-Ko. Kor J Herbol. 2019;34:41–7.

[50] Lee ES, Seo BI, Lee JU, Bae JS. The immunological activities of Kyungokgao and prescription of modified Kyungokgao. Kor J Herbol. 2002;17:95–100.

[51] Im LR, Ahn JY, Kim JH, et al. Inhibitory effect of Kyungokgao in the development of 2,4-dinitrochlorobenzene-induced atopic dermatitis in NC/Nga mice. Arch Pharm Res. 2011;34:317–21.

[52] Do EJ, Hwang MY, Kim SY, et al. The effect of Gungokgog-Gamibang extract on hair growth and protein expression in mice. Kor J Herbol. 2011;26:69–14.

[53] Cha YY. A comparative study on effects of kyungokgog and kyungokgog Ga Nokkyong on growth in growth deficiency rat with insufficient nutrition diet. J Korean Obes Res. 2009;9:59–69.

[54] Han SH, Cha YY, Lee E. Effects of kyungokgog [琼玉膏] on growth and learning ability in growth deficiency rat with insufficient nutrition diet. J Korean Rehabil. 2008;18:97–109.

[55] Jung BK, Yun HJ, Lee YJ, Kang MS, Baek JH. The effect of KyungOcGamibang on the growth of the rats. J Pediatr Korean Med. 2009;25:141–58.

[56] Kim TH, Lee KM, Hong ND, Jung YS. Anti-platelet and anti-thrombotic effect of a traditional herbal medicine Kyung-ok-Ko. J Ethnopharmacol. 2016;178:172–9.

[57] Kim JB, Song HN. Effects of Kyeongok-go and its two added precriptions on hyperlipidemic rats induced by high-fat diet. J Physiol Pathol Korean Med. 2014;30:68–71.

[58] Whang WK, Oh IS, Lee SH, Choi SB, Kim IH. The physiological activities of Kyung OK-KO (II) – effects on the hyperglycemia, hypertension, anti-fatigue and decrease of body weight. Korean J Pharmacogn. 1994;25:51–8.

[59] Shin SH, Yang KS. Protective effects of Qiongyuogao on oxidative stress-induced apoptosis of H9c2 cardiomyoblast cells. J Korean Med. 2004;25:149–59.
[60] Wen S. Experimental study on laxative action of Qiongyu Gao in mice. J Guangzhou Univ Trad Chin Med. 1995;12:36–9.

[61] Chen XY, Shen Q, Tang CZ, Gu JH. Experimental study on protective effect of Qiongyuagao on gastric mucosa. [琼玉膏保护胃粘膜作用的实验研究]. New Chin Med. 2008;32:36–7.

[62] Whang WK, Oh IS, Kim YB, Shin SD, Kim IH. The physiological activities of KYUNGOKKO (Ⅲ) – effects on inflammation, gastric ulcer, analgesic and Homothermics. Korean J Pharmacogn. 1994;25:153–9.

[63] Hu JR, Jung CJ, Ku SM, et al. Anti-inflammatory, expectorant, and antitussive properties of Kyeongok-goin ICR mice. Pharm Biol. 2021;59:321–34.

[64] Jeon SB, Jung HJ, Jung SK, Rhee HK. Experimental studies of the effects of Kyungok-go against mycobacteria tuberculosis. J Int Korean Med. 2000;21:555–63.

[65] Hwang YH, Kim KJ, Kim JJ, et al. Antiestoporosis activity of new oriental medicine preparation (Kyungokko mixed with water extract of Hovenia dulcis) on the ovariectomized mice. Evid Based Complement Alternat Med. 2015;2015:373145.

[66] Kim JH, Lee JH, Oh JM, Kim YK. Inhibitory effects on bone resorption and osteoblast proliferation of Kyungok-Go. Herb Formula Sci. 2011;19:61–71.

[67] Kwon WJ, Kim IH. Effect of concurrent administration of Kyung Ok Ko and glutathione on CC1_4-induced liver lesion in rats = studies on the concurrent administration of medicines (X). Chung-Ang J Pharm Sci. 1992;6:13–20.

[68] Kim YA, Jin SW, Kim SM, et al. Anti-fatigue effect of Kyung-ok-Ko. Korean J Pharmacogn. 2016;47:238–63.

[69] Wu SJ, Ng LT, Lin CC. Antioxidant activities of some common ingredients of traditional Chinese medicine, Angelica sinensis, Lycium barbarum and Poria cocos. Phytother Res. 2004;18:1008–12.

[70] Zhang R, Kang KA, Piao MJ, et al. Cytoprotective effect of the fruits of Lycium chinense Miller against oxidative stress-induced hepatotoxicity. J Ethnopharmacol. 2010;130:299–306.

[71] Park HJ, Shim HS, Choo WK, Kim KS, Bae H, Shim I. Neuroprotective effect of lycium chinense Fruit on trimethyltin-induced learning and memory deficits in the rats. Exp Neurobiol. 2011;20:137–43.

[72] Zhang Y, Wang W, Zhang J. Effects of novel anxiolytic 4-butyl-alpha-agarofuran on levels of monoamine neurotransmitters in rats. Eur J Pharmacol. 2004;504:39–44.

[73] Zheng QL, Zhu HY, Xu X, et al. Korean red ginseng alleviate depressive disorder by improving astrocyte gap junction function. J Ethnopharmacol. 2021;281:114466.

[74] Lee JH, Jo DC, Kim CG, et al. A literature review of effectiveness on the Gongjin-dan(Gongchen-dan). J Korean Rehabil. 2013;23:69–78.

[75] Nordmann R, Ribiere C, Rouach H. Ethanol-induced lipid peroxidation and oxidative stress in extrahepatic tissues. Alcohol Alcohol. 1990;25:231–7.

[76] Pozzi R, De Berardis B, Paololetti L, Guastadisegni C. Inflammatory mediators induced by coarse (PM2.5-10) and fine (PM2.5) urban air particles in RAW 264.7 cells. Toxicology. 2003;183:243–54.

[77] Kim HJ, Bae JT, Lee JW, Hwang BMH, Im HG, Lee IS. Antioxidant activity and inhibitive effects on human leukemia cells of edible mushrooms extracts. Korean J Food Preserv. 2005;12:80–5.

[78] You JS, Li CY, Chen W, et al. A network pharmacology-based study on Alzheimer disease prevention and treatment of Qiong Yu Gao. BioData Min. 2020;13:2.

[79] Qi L, Luo Q, Zhang Y, Jia F, Zhao Y, Wang F. Advances in toxicological research of the anticancer drug cisplatin. Chem Res Toxicol. 2019;32:1469–86.

[80] Crona DJ, Faso A, Nishijima TF, McGraw KA, Galsky MD, Milowsky MI. A systematic review of strategies to prevent cisplatin-induced nephrotoxicity. Oncologist. 2017;22:609–19.