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Review

Adjuvant herbal therapy for targeting susceptibility genes to Kawasaki disease: An overview of epidemiology, pathogenesis, diagnosis and pharmacological treatment of Kawasaki disease

Bin Tang, Hang Hong Lo, Cheng Lei, Ka In U, Wen-Luan Wendy Hsiao, Xiaoling Guo, Jun Bai, Vincent Kam-Wai Wong, Betty Yuen-Kwan Law

Abstract

Background: Kawasaki disease (KD) is a self-limiting acute systemic vasculitis occur mainly in infants and young children under 5 years old. Although the use of acetylsalicylic acid (AAS) in combination with intravenous immunoglobulin (IVIG) remains the standard therapy to KD, the etiology, genetic susceptibility genes and pathogenic factors of KD are still un-elucidated.

Purpose: Current obstacles in the treatment of KD include the lack of standard clinical and genetic markers for early diagnosis, possible severe side effect of AAS (Reye's syndrome), and the refractory KD cases with resistance to IVIG therapy; therefore, this review has focused on introducing the current advances in the identification of genetic susceptibility genes, environmental factors, diagnostic markers and adjuvant pharmacological intervention for KD.

Results: With an overall update in the development of KD from different aspects, our current bioinformatics data has suggested CASP3, CD40 and TLR4 as the possible pathogenic factors or diagnostic markers of KD. Besides, a list of herbal medicines which may work as the adjunct therapy for KD via targeting different proposed molecular targets of KD have also been summarized.

Conclusion: With the aid of modern pharmacological research and technology, it is anticipated that novel therapeutic remedies, especially active herbal chemicals targeting precise clinical markers of KD could be developed for accurate diagnosis and treatment of the disease.

Introduction

With the 1st suspected case reported in 1967 (Kawasaki, 2002), KD was identified as an acute pediatric systemic vasculitis with clinical symptoms such as sustained fever, oral mucosal lesions, pleural rash, swollen cervical lymph nodes, conjunctival hyperemia, severe swelling of hand and foot with skin peeling on fingertips. One of the most serious sequelae of KD is the inflammation of the heart arteries which lead to the formation of aneurysm and coronary artery lesions (CALs) (Denby et al., 2017). Besides, KD was reported to affect many different organ systems including blood vessels, mucous membranes, skins and lymph nodes (Kuwabara et al., 2015). With 85% of cases occur in children under 5 years old, surveys have indicated that CALs caused by KD, is gradually replacing rheumatism as the most common acquired heart disease of childhood in developed countries (Dimitriades et al., 2014). Although the cause of KD remains unclear, effective IVIG intervention within the therapeutic window can lower the rate of CALs formation from 25% to less than 5% (Kuwabara et al., 2015). It is...
noteworthy that in recent years, a subtype of KD, the KD shock syndrome, were also reported for its severity and correlation to the coronary artery abnormalities and IVIG resistance (Gamez-Gonzalez et al., 2018). Therefore, early diagnosis and treatment of KD are particularly important. Although recent advances in the understanding of KD symptoms and treatments have substantially reduced the rate of complication of the disease, considerable efforts are required to characterize the causative cause, genetic and serological markers correlated to the pathogenesis, diagnosis and intervention of KD.

The regional and seasonal variation in the epidemiology of KD

Although with an increasing trend of KD incidence, the risk factors responsible for the current increase in cases remain unclear (Singh et al., 2015). Japan, Korea and Taiwan were regions on the list of highest incidence rate of KD (Singh et al., 2015). In Japan, according to the nationwide survey conducted in 1996, the estimated incidence rate of KD was 120-150 cases per 100,000 children under 5 year old (Burns et al., 2000). According to the 2017 KD national epidemiological survey in Japan, with an average number of 5000–6000 new cases each year, the total number of KD cases have reached 362,710 (male: 209,508 and female: 153,202) (Japan, 2017). At 2014, the incidence of KD in Korea were 194.7 per 100,000 children under 5 year old (Kim et al., 2017a). Although national occurrence of KD was reported in past years, seasonal peaks of KD incidence were also reported in many geographic regions (Burns et al., 2000). For example, the peak of KD incidence occurs in January and July in Japan, while in mainland China and Taiwan, the peak of KD incidence was reached from December to January and June to July. In USA, Canada, Australia and Europe, while a higher of KD incidence rate was observed during the winter months (Iha et al., 2016; Singh et al., 2015), no significant seasonal variation of KD was reported in Korea (Rhim et al., 2019; Rhim et al., 2014). With an overall higher incidence rate of KD in males than in females, the male-to-female ratio was about 1.33, 1.42 and 1.62 in Japan, Korea, and Taiwan, respectively (Ha et al., 2016; Lue et al., 2014; Singh et al., 2015).

Evolutionary change in the diagnostic criteria of KD

According to the American Heart Association (AHA) diagnostic guidelines (2004) and the international symposium diagnostic guidelines (2002), 6 classic clinical symptoms and criteria for the diagnosis of KD are listed (Ayusawa et al., 2005; Sagull et al., 2015). As a general principle, continued high fever (> 39 °C) lasting for at least 5 days with no response to antibiotics and antipyretics, with the development of at least 4 out of 5 listed classic diagnostic symptoms including polymorphous rash, conjunctivitis, cervical lymphadenopathy, changes in oral or extremities, could be diagnosed as KD (Kuo et al., 2015b). In addition to the assessment on clinical symptoms, laboratory diagnosis of cardiovascular damages such as chest X-ray findings, electrocardiogram changes, auscultation, aneurysm of peripheral arteries other than coronary, 2D echocardiography, angina pectoris or myocardial infarction are also important supplements for the diagnosis of KD (Ayusawa et al., 2005; Sagull et al., 2015). Other supplementary diagnostic references such as platelets counts are also applied for the diagnosis of suspected cases of KD (Ruan et al., 2013). In fact, the diagnostic guidelines for KD have been revised for 5 times in Japan, and with its major changes listed in Table A. Now, the 2005 diagnostic guidelines (5th revision) are commonly used for the diagnosis of KD in Japan. With the current diagnostic guidelines set by the AHA in 2017, the diagnostic criteria in US has been revised for 3 times since 2004, and with its major changes listed in Table B. Besides, Korea, China and Europe are countries which have adopted the AHA guidelines (2017) as the reference to the diagnosis of KD. Although with standardized diagnostic criteria compiled, due to variability of clinical symptoms in different cases, discrepancies in the interpretation of clinical signs and symptoms have led to undiagnosed and unreported cases of KD (Ayusawa et al., 2005; Daniels et al., 2012). However, recent report has suggested the evaluation on the systemic inflammatory parameters such as C-reactive protein (CRP), neutrophil differential, albumin and hemoglobin in the early phase of acute KD, are critical for the early diagnosis of KD (Seo et al., 2018). Consistently, additional study has suggested the increased level of immunoglobulin and platelets in the recovery phase of KD, may indicate the degree of systemic inflammation in acute KD (Han et al., 2017).

Although the therapeutic strategy for different types of KD remains the same, cases of KD are classified into stereotype, non-stereotype and incomplete type according to the clinical symptoms of patient. In Japan, in accordance with the 2005 diagnostic guidelines (5th revision), KD patients are divided into 3 different types: (1) Complete KD with at least 5 developed classic KD symptoms, including (i) fever persisting for 5 days or more (inclusive of cases in whom the fever has subsided before the 5th day in response to therapy), (ii) bilateral conjunctival congestion, (iii) changes of lips and oral cavity such as reddening of lips, strawberry tongue, diffuse injection of oral and pharyngeal mucosa, (iv) polymorphous exanthema, (v) changes of peripheral extremities progressing from reddening of palms and soles, edema to the convalescent stage of membranous desquamation from fingertips, (vi) acute non-purulent cervical lymphadenopathy; (2) Incomplete KD with sustained fever for 5 days which was accompanied by 2 or 3 classic KD symptoms, together with the diagnosis based on 2D echocardiography or coronary angiography to rule out the possibility of other diseases; (3) Atypical KD according to doctor’s evaluation on patients with no more than 4 classic KD symptoms, but accompanied by acute diarrhea, upper airway obstruction, proteinuria, nephritis, shock, massive lymphadenopathy, meningitis, blindness, intermittent deafness or other clinical symptoms (Ayusawa et al., 2005).

Based on the statistics of the national epidemiological survey of KD in Japan at 2017, the percentage of stereotype and non-stereotype of KD were 77.8% and 1.6% respectively, while 20.6% of cases were referred as incomplete type (Japan, 2017). It is noteworthy that there is an increasing incidence of incomplete KD case reported with mild symptom, a lower incidence of CALs, decreased count on CRP and platelet, together with an increased level of albumin and hemoglobin when compared to previous cases (Kil et al., 2017). All these have suggested that advances in the diagnosis of incomplete KD, such as by evaluating the presence of anterior uveitis symptoms (Lee et al., 2016), are needed to facilitate the precise identification of KD patients for early IVIG treatment to minimize undiagnosed cases.

Pathogenesis of KD: from ambient environment to immunology and genetic regulation

KD is highly correlated to the increased level of circulating inflammatory and immune cells which infiltrate into the vascular endothelial cells via systemic vasculitis. Instead of contributing by a single gene, multiple genes regulating inflammatory, cardiovascular and immune responses were reported to be associated with the pathogenesis of KD (Kuo et al., 2015b). Further studies have shown that KD may be triggered by pathogenic microbial or viral infections, leading to inflammatory and immune responses mediated by T cells, and ultimately the destruction of vascular endothelial function with inflammatory lesions (Rowley et al., 2008).

Regional dietary and environmental factors contributing to KD

With the increasing incidence of KD in recent years, the role of environmental factors on the epidemiology of KD has been investigated. Rodo et al. suggested the northeastern China may be a source for the wind-borne pathogen of KD in Japan (Rodo et al., 2014). Other studies suggested the incidence of KD in Shanghai of China was increased with the exposure to high temperature and was independent to the factor of
Evolution of diagnostic guide for KD in Japan from 1970 to 2005.

| Year | Evolution in the major changes of diagnostic criteria for KD | References |
|------|-------------------------------------------------------------|------------|
| 1978 | 1) Fever lasts for 1–2 weeks and with no therapeutic effect after antibiotic treatment. 2) Bilateral conjunctival hyperemia. 3) Lip and oral changes: dry lips, redness, cleft palate, tongue nipple bulge, diffuse oral and pharyngeal mucosa. 4) Changes in extremities: In the early stage of the disease, redness of the palm of the hand and hard swelling of the hands and feet, membranous peeling of the metatarsal (toe) end. 5) Erythema of the trunk, but no blistering and scarring. 6) The lymph nodes are non-suppurative and grown up to ≥ 1.5 cm in diameter. | Kawasaki et al., 1974 |
| 1984 | 1) Modified the fever period from 1~2 weeks to 5 days or above. 2) Specified the number of KD symptoms that were diagnosed (at least 5 of 6 items should be confirmed). 3) Supplementary information such as 2D echocardiogram or coronary angiography which can confirm the diagnosis of coronary aneurysm or coronary artery dilatation (with 4 major symptoms being diagnosed). | Kim, 2006 |
| 1988 | 1) The criteria of persistent fever continued for 5 days or more as a prerequisite for KD diagnosis. 2) 4 out of 5 diagnosis criteria are confirmed. 3) Based on the above conditions, the possibilities of other diseases need to be excluded to confirm the diagnosis. | O'Loughlin, 1989 |
| 2002 | 1) Persistent fever is observed for 5 days or more in parallel with the occurrence of 5 main symptoms as the basis for the diagnosis of KD. 2) The patient who has sustained fever for less than 5 days can also be diagnosed as KD if typical symptoms are shown. 3) Diagnosis according to the additional reference based on supplementary symptoms or manifestations. 4) Emphasize the importance of clinical diagnosis of incomplete KD, which the main symptom compliance rate does not meet the full KD diagnostic requirements. 5) KD can also be diagnosed if the possibilities of other diseases are ruled out, and when a patient has confirmed with the development of coronary aneurysm or coronary artery dilatation. | Jane et al., 2003 |
| 2005 | 1) The diagnostic criteria in cases with 4 or less febrile days after early IVIG treatment are proposed to be the same as the cases with 5 or more febrile days. 2) Emphasize the clinical importance on the diagnosis of atypical (incomplete or suspicious) cases. 3) The order of 6 principal symptoms of KD was rearranged as (i) Fever (ii) Conjunctival congestion (iii) Changes of lips and oral cavity (iv) Rash (v) Changes of extremities (vi) Cervical lymphadenopathy. | Ayusawa et al., 2005 |

Air pollution (Lin et al., 2017; Zeft et al., 2016). In Taiwan, prolonged exposure to ozone was associated with a higher risk of KD (Jung et al., 2017). Recent studies have also depicted various dietary factors are interlinked with the pathogenesis of KD. For example, the consumption of soy was correlated to a higher risk of KD (Portman et al., 2016). Further pediatric research indicated that the intake of isoflavone beyond the age of conferred maternal immunity, instead of maternal-fetal transmission of isoflavones, is correlated to the higher incidence of KD in Asia than in Western countries which have relatively lower soy or isoflavone consumption (Portman, 2013). In Korea, report has postulated the pathogenesis of KD may be triggered by the variants in normal flora of genetically susceptible children, which are highly related to environmental factors. Therefore, all these may help to explain the epidemiological and regional characteristics of KD (Lee et al., 2007).

Table B
Evolution of diagnostic guide for KD in America from 1978 to 2017.

| Year | Evolution in the major changes of diagnostic criteria for KD | References |
|------|-------------------------------------------------------------|------------|
| 1978 | This standard is similar to the KD diagnostic standard of Japan in 1988. The diagnostic criteria include continuous fever for ≥5 days, possess 4 out of 5 major symptoms of KD, and with the possibilities of getting other diseases being ignored. | Burns et al., 1984 |
| 2004 | In this diagnostic guide, fever lasts for longer than 5 days is an essential diagnostic criterion for KD. If there are 4 main symptoms appeared in addition to fever, typical KD can be diagnosed even the fever lasted for only 4 days. More importantly, the necessary on the diagnosis and revision of the diagnosis criteria of incomplete KD were emphasized. Also, the diagnosis procedures and evaluation of incomplete KD suspected cases were proposed. | Newburger et al., 2004 |
| 2017 | 1) For the first time the coronary artery anomaly was evaluated by the Z-value, i.e. the body surface area corrected coronary lumen diameter. 2) Patients with recovery from fever lasting for ≥7 days should not be excluded from KD diagnosis. 3) The diagnosis process on incomplete KD is simplified when compared to the 2004 version, i.e. if the child has fever ≥ 5 days and fulfills 2 or 3 diagnostic criteria, or has fever for ≥7 days without other confirmed reasons, can also be diagnosed as KD with the support of clinical laboratory test results. 4) 5 clinical observations are proposed for the consideration of diagnosis of KD (i) Baby less than 6 months with prolonged fever and irritability (ii) Long-term fever in infants with unexplained aseptic meningitis (iii) Infants or children with prolonged fever and unexplained or culture-negative shock. (iv) Infants or children with prolonged fever and cervical lymphadenitis but no response after antibiotic treatment (v) Long-term fever in infants or children after antibiotic treatment towards cellulitis in pharynx. 5) It is proposed that elevated N-terminal B-type brain natriuretic peptide (NT-BNP) only suggests cardiac involvement but cannot be used for KD diagnosis. 6) It is suggested that KD patients with shock are prone to IVIG resistant, coronary artery complications, mitral regurgitation, prolonged myocardial insufficiency and other clinical manifestations. | Saguil et al., 2015 |

**Linking up various infectious agents with the pathogenesis of KD**

With the fact that most of the clinical symptoms such as fever, rash, conjunctivitis, cervical lymphadenopathy, and the epidemiological and laboratory characteristics of KD are similar to the classical symptoms of inflammation (Ayusawa et al., 2005; Ha et al., 2016; Japan, 2017; Lue et al., 2014; Saguil et al., 2015; Singh et al., 2015), therefore, KD is also suggested as an infectious disease. However, there is still no definite test to differentiate KD from other diseases such as scarlet fever, juvenile rheumatoid arthritis, toxic shock syndrome or measles that cause similar symptoms (Maconochie, 2004; Pilania and Singh, 2020; Rowley and Shulman, 1998). Therefore, physical examination and tests such as urine and blood tests, electrocardiogram and echocardiogram are required for the diagnosis of KD. AHA has published the supplemental laboratory criteria on the level of CRP, white blood cell,
hemoglobin, platelet, serum albumin, alanine aminotransferase and urine white blood cell for the diagnosis of incomplete KD, these laboratory characteristics have implied that infection factors are closely related to KD (Saguil et al., 2015). However, as the infectious factors of KD remains un-elucidated, classical methods such as microbiol culture, microscopy and polymerase chain reaction are still not commonly applied for the diagnosis of KD. Consistent with the seasonal cycles of infectious diseases, the epidemiological characteristics and the incidence of KD were disparate in different seasons (Ha et al., 2016; Japan, 2017; Lue et al., 2014; Singh et al., 2015). According to the available data, there were 3 large-scale national epidemic outbreaks of KD in Japan at 1979, 1982 and 1986, respectively (Japan, 2017).

Studies have reported the possible microbes or microbe-derived substances that may cause the pathogenesis of KD, such as rickettsia-like agent, chlamydia pneumoniae, mycoplasma pneumoniae, rickettsia organisms, proteobacterium acne, leptospira spp, yersinia pseudotuberculosis, retrovirus, measles, chickenpox, human herpesvirus 6, cytomegalovirus, group A streptococcus, dengue fever virus, Epstein-barr virus, coronavirus, parvovirus B19, bacillus cereus, human bocavirus, staphylococcus, staphylococcal or streptococcal superantigens (Chang et al., 2014; Rowley et al., 2008). A recent report by Rhim et al. has suggested a presumed etiology of KD which may be associated with the pathogens of acute pyelonephritis and exanthem subitum (Jung-Woo et al., 2019). Furthermore, Jordan et al. reported that up to 8.8% of KD children had acquired upper respiratory tract infection simultaneously (Jordan-Villegas et al., 2010). Therefore, the report has suggested the prescription of IVIG therapy to suspected KD children without classic clinical symptoms but with recorded respiratory viral infections. Some studies have suggested the human adenovirus (HAdV) as one of the pathogens triggering KD (Fukuda et al., 2017; Jaggi et al., 2013). For example, Fukuda et al. reported the case of 1 monozygotic twins who have been sequentially diagnosed with KD in conjunction with HAdV-3 infection (Fukuda et al., 2017). Jaggi et al. reported 77 cases of KD patients were diagnosed with HAdV infection by quantitative polymerase chain reaction (Jaggi et al., 2013). Although with the close correlation between various infectious factors and KD, unlike other childhood infectious diseases with known infectious factors or vaccines, the infectious agent contributing to the pathogenesis of KD remains un-characterized and more studies are required.

**Immunopathogenesis of KD**

Immunological abnormalities with the development of coronary artery lesions were involved in the pathogenesis of KD. It was proposed by Lee et al. that the immunopathogenesis of KD is based on a “protein homeostasis system” that controls the pathogenic toxic proteins which spread and bind to endothelial cells of coronary arteries, with the involvement of non-specific T cells and non-specific antibodies to produce various cytokines contributing to endothelial cell injury (Lee et al., 2012a). While both the innate and acquired systems are activated after pathogen infection, clinical and laboratory studies have found that the occurrence of KD is related to the activation of the innate immune system (Hara et al., 2016). Broderick et al. reported 4 cases of KD with the reoccurrence of inflammatory clinical symptoms similar to those in “recurrent fever syndrome” existed in febrile disease due to the dysregulation of innate immune system (Broderick et al., 2011).

The acquired immune system has both cell-mediated immunity and humoral immunity. The cell-mediated immunity activates macrophages, T cells (cluster of differentiation (CD) 4+ or CD8+) and releases lymphokines. Rowley et al. showed that chronic coronary arteritis in KD continued long after the onset of the disease via upregulation of T lymphocyte and type I interferon genes (Rowley et al., 2017). Other studies reported the increased plasma level of T helper cell type (Th) 1 cytokines (interferon-γ, interleukin (IL)-2) and Th2 cytokines (IL-4 and IL-10) during the acute stage of KD (Lee et al., 2015b), suggesting that both Th1 and Th2 cells may be activated simultaneously during the acute stage of KD. In recent years, with the research focus on identifying the key cytokines responsible for KD, tumor necrosis factor (TNF) and IL-1 have just been reported to play temporally roles in acute cardiac inflammation and the development of coronary vasculitis, respectively, which suggested the possible immunopathogenesis of KD (Stock et al., 2019).

**Ethnic disparities in genetic susceptibility to KD**

Recently, more evidence has suggested KD as a genetic disease. According to the 2017 epidemiological survey in Japan, the incidence rate of KD was 2.1% and 1.2% higher in children with siblings or parents, who have been diagnosed with KD (Japan, 2017). Besides, the incidence of KD was higher in Asian population, especially Japanese (Singh et al., 2015), suggesting the pathogenesis of KD caused by the abnormal immune cascade triggered by infection, may be correlated to the susceptibility of genes. On account of more monozygotic twins have been diagnosed with KD, genetic studies on the susceptibility gene loci of KD have been performed by using the candidate genes or genome-wide association method (GWAS) (Onouchi, 2009).

**Candidate genes and genome-wide association studies of KD**

Candidate genes method refers to the selection of a potential site from a known gene based on the reported pathological or physiological processes of a specific disease, examined by the correlation analysis (Lv et al., 2013). Previous studies of candidate genes in KD were summarized in Table C (Kim and Kim, 2016; Lv et al., 2013). This approach has been used to identify SNPs in Parkinson’s disease (Witoelar et al., 2017), Crohn disease (Foo et al., 2017), diabetes (Bush and Moore, 2012), and heart abnormalities (Bush and Moore, 2012). Consistently, a SNP within ITPKC gene was highly associated with the development of coronary artery abnormalities and KD (Onouchi, 2009). However, findings suggested that SNPs of ITPKC susceptibility in KD may vary for different ethnicities, for example, in Japan, SNP (rs28493229) in ITPKC was associated with risk of coronary artery abnormalities, while the same ITPKC SNP in Chinese was associated with susceptibility of KD (Yang et al., 2012). In the European population, several genes such as calcium/calmodulin-dependent protein kinase type II delta chain, cub and sushi multiple domains 1, diacylglycerol kinase beta, E3 ubiquitin-protein ligase, N-acetylated alpha-linked acidic dipeptidase-like 2, protein phosphatase 1 regulatory subunit 14C, T-complex protein 1 subunit alpha, zinc finger homeobox 3, melanoma inhibitory activity/ras-related GTP-binding protein 4b, ITPKC (Burgner et al., 2009; Khor et al., 2011), Fe fragment of immunoglobulin G, low-affinity II a (FCCR2A), have been identified as susceptibility genes for KD through GWAS (Khor et al., 2011).

Further researches have also suggested the susceptibility genes for KD are correlated to ethnicity. For example, SNPs in B lymphocyte kinase, nicotinamide mononucleotide adenyllytransferase 2, HLA class I histocompatibility antigen protein P5 and nod-like receptor family pyrin domain containing 14 were identified as susceptibility loci for pathogenesis of KD in Korean population (Kim et al., 2017b). Besides, SNP located at the CRP locus (rs12068753) was found highly correlated to the CRP levels of KD patients in Korea (Kim et al., 2015). Susceptible gene locus associated with KD such as protein pellino homolog 1 (Kim et al., 2012b), Lp31 (Kim et al., 2011), coatomer subunit beta, endoplasmic reticulum aminopeptidase 1, immunoglobulin heavy-chain variable, BLK, human leukocyte antigen (HLA) (Oh et al., 2008),
Cardiovascular function related genes
CD40, CD40L, ETN, ITPKC, TGBFR2, ABO, PEL1, SMAD3, TGBFR2, CASP3, VEGFA, MHC, MICA, IL10, IL4, IL-18, CCLI4, MMP2, MMP3, MMP9, MMP12, FGF, MMP3, PRRC2A, ABHD16A, ITPRC, COLL12A, MLF2, MIF, TFB1M, HLA-E, TIPM4, TNF, MMP13, TIPM2, ACE, KDR, CD40LG, AGTR1, CD44, MTHFR, FGR2B, FCGR3A, FCGR3B, IL-1β, VEGFR2, LTA, TNF-α, eNOS, iNOS, MBL, CD40, cluster of differentiation 209; NOD1, nucleotide-binding oligomerization domain-containing protein 1; NLRP1, NACHT, LRR, FIIND, CARD domain and PYD domains-containing protein 1; ANGPT1, angiopoietin 1; MSH5, Muts protein homolog 5; VWA7, von willebrand factor a domain containing 7; TNFRSF1A, tumor necrosis factor receptor 1; CCLI4, chemokine (C-C motif) ligand 3-4; MMP1, matrix metalloproteinase-11; PDCD1, programmed cell death protein 1; IL18, interleukin-18; HLA-A, human leukocyte antigen A; HLA-B, human leukocyte antigen B; HLA-C, human leukocyte antigen C; CCR3, C-C chemokine receptor type 3; CCR2, C-C chemokine receptor type 2; IL1RN, Interleukin 1 receptor antagonist; IL4, Interleukin 4; 4SCCLI1A, natural resistance-associated macrophage protein 1; LTA, lymphotoxin alpha; alpha; HLA-DQB2, HLA class II histocompatibility antigen, DX beta chain; HLA-DOB, HLA-DQ beta chain; MPO, myeloperoxidase.

Bioinformatics analysis on genes responsible for the pathophysiology of KD
To summarize and integrate the genes responsible for the pathogenesis of KD, we have further analyzed the KD-related genes reported by literatures from 1970 to 2018. Among them, 25 KD related pathways and 229 KD related genes were sorted out and input to the software Cytoscape enrichment plugin, with a genetic network summarized in Fig. A. According to the enrichment score of DAVID, 3 genes including toll-like receptor 4 (TLR4), caspase 3 and CD4 are identified as the most enriched genes for KD. Firstly, TLR4 is one of toll-like receptors which level was found upregulated on peripheral blood mononuclear/macrophage cells in acute KD patients when compared to healthy children of the same age (Wang et al., 2008). Together with the elevated expression of related molecules myeloid differentiation protein-2 and myeloid differentiation factor 88 (MyD88), it was suggested that abnormal activation of TLR4 may be one of the initiating factors leading to immune dysfunction in KD patients, which also involved the activation of the nuclear factor κB (NF-κB) and its downstream pathway with the excessive production of pro-inflammatory cytokines such as TNF-α (Wang et al., 2008).

Consistent with our bioinformatics data, CASP3 is reported to be associated with the formation of coronary lesions in KD patients (Onouchi et al., 2011). Besides, other than its basic role in triggering apoptosis, the interaction of CASP3 with the T cell receptor, was correlated to the increased transcription of CASP3 and activation of the nuclear factor of activated T-cells signaling pathway, accompanied by the increased level of cytokines such as IL-2 (Onouchi et al., 2010; Wu et al., 2006). With the fact that there are different protein substrates for CASP3, therefore, further investigation on the immuno-regulatory role of CASP3 in the pathogenesis of KD is highly desired. Literature has also showed that the expression level of CD40 was significantly higher in both acute KD and KD with coronary artery lesion groups, suggesting the possible immunological role of CD40 in the pathogenesis of KD, which may be modulated through the MyD88-independent-Toll-like receptor 4 transduction pathway (Wang et al., 2007). Collectively,
together with the literatures supporting the pathogenic roles of different genes in KD, the current bioinformatic data may provide useful information for the searching of potential drug targets, gene markers or regulatory pathways of KD, which provide practitioners or researchers in the field with clue for further investigation.

Limitations and side effects of the combined therapy of IVIG and AAS

Until now, while the etiology of KD remains un-elucidated, the therapy for all types of KD is still limited on the combinational use of IVIG and AAS at different stages of KD. In IVIG resistance or refractory KD, clinicians may need to apply a second dose of IVIG, with additional treatment designated for anti-vascular inflammation (Newburger et al., 2004). Reports have depicted around 25–30% of untreated KD patients developed CALs including coronary artery dilation, aneurysms or fistula formation (Kuo et al., 2015b). However, approximately 10% of KD patients did not respond to IVIG treatment, and eventually led to a higher risk of CALs formation or KD shock syndrome (Burns and Glode, 2004; Gamez-Gonzalez et al., 2018; Kuo et al., 2015b).

Combined therapy of IVIG and AAS administered for reducing the incidence of coronary artery abnormalities, anti-inflammatory and anti-platelet in the acute phase of KD, has been adopted as a standard KD therapy for many years (Shulman and Rowley, 2015). The prevalence of coronary abnormalities was inversely related to the total dose of IVIG and independent of the dose of AAS (30–50 mg/kg per day in Japan and 80–100 mg/kg per day in North America) during the acute phase (Terai and Shulman, 1997).

The prognosis of IVIG resistance

IVIG resistance was defined as the persistent fever for 48 h after completion of IVIG treatment (Singer et al., 2008). About 10–20% of KD patients were reported as not responsive to the treatment of IVIG and high-dose AAS, and with a higher risk of developing coronary heart disease complications (Singer et al., 2008). Some reports have suggested several biomarkers and genetic polymorphisms can be applied to predict resistance to IVIG such as clusterin (Ou-Yang et al., 2013), IL-6 (Sato et al., 2013), IL-10 (Wang et al., 2013), IL-17 (Jia et al., 2010), TNF-α (Wang et al., 2013), and CD4+ CD25+ forkyhox P3 regulatory T cells (Jia et al., 2010). Some laboratory indicators are also important for the prediction of IVIG responsiveness, for example, age, sex, number of illness days, platelet count, erythrocyte sedimentation rate, aspartate aminotransferase, hemoglobin concentration, CRP, eosinophil, total bilirubin, lactate dehydrogenase (Kuo et al., 2007; Sleeper et al., 2011), cholesterol (Hashwani et al., 2011), serum albumin (Lee et al., 2015a), percentage of neutrophils, and serum sodium level (Moon et al., 2016). Although there are still no definite treatments for KD patients with IVIG resistance, steroid such as prednisolone was reported to reduce the incidence of coronary abnormalities (Miyata et al., 2018). Infliximab (Son et al., 2011), methotrexate (Lee et al., 2008) and plasma exchange (Hokosaki et al., 2012) have also been reported to benefit KD patients with initial IVIG treatment failure. Among them, infliximab was reported to process good adjuvant efficacy for KD patients with IVIG resistance by reducing duration of fever, improving IVIG reaction rate and level of specific inflammatory marker. This observation is consistent with the results of several independent clinical trials in different countries. For example, in Japan, the use of infliximab was correlated with the level of several transcripts associated with IVIG resistance factors and inflammation signaling pathways of KD such as peptidase inhibitor-3, matrix metalloproteinase-8, chemokine receptor-2 and pentamer-3 (Ogihara et al., 2014). In Korea, retrospective analysis of 16 patients with refractory KD indicated that infliximab can also be used to prevent the progression of CAL in the refractory KD (Song et al., 2010).

Reye's syndrome

The possible adverse effect resulting from the standard AAS treatment after IVIG therapy is the risk of developing Reye's syndrome (RS)
in KD patients (Belay et al., 1999; Remintong et al., 1985). RS occurs during the treatment of fever with drugs containing AAS, and is usually preceded by a viral infection, especially influenza and chickenpox, in children and teenagers, leading to possible lethal side effects such as toxic encephalopathy or liver dysfunction (Chornomydzy et al., 2017). The surveillance of RS was first started in the U.S. at early 1970s and has led to the restricted use of AAS in children nowadays (Chapman and Arnold, 2020). Besides, according to the AHA diagnostic guidelines of KD (2017), KD patients who have been prescribed with high dose of AAS treatment are at the possible risk of getting RS, and therefore replacing the AAS with another antiplatelet drug is recommended (McCrindle et al., 2017). In Japan (Nejihashi et al., 1980), Taiwan (Wei et al., 2005), Hong Kong (Su et al., 2018) and the United States (Belay et al., 1999), although only occasional RS cases were reported, finding an alternative anti-inflammatory drug or herbal compounds that replaces AAS is desirable.

**Herbal chemicals as the effective adjuvant therapy to KD**

In fact, many studies have proposed the use of traditional Chinese medicines (TCMs) or natural products as a supplementary therapy for the KD (Table E). For example, resveratrol from *Vitis vinifera* L. (fruit) possesses anti-inflammatory effects on human coronary arterial endothelial cells via decreasing the level of TNF-α-induced expression of intercellular adhesion molecule-1, inducible nitric oxide synthase and IL-1β and autophagy (Huang et al., 2017). Besides, low dose of resveratrol could protect against experimental induced RS partially via inhibition of oxidative stress and restoration of complex I activity (Abdin and Sarhan, 2014). Based on the above observation, natural product may work as a possible supplement for applying with AAS in infants and young children to reduce the risk of RS or other side effect. On the other hand, triptolide from *Tripterygium wilfordii Hook f.* (root) could reduce the expression of intercellular adhesion molecule-1 in endothelial cells and increase the rate of apoptosis of inflammatory cells in a mouse model of KD (Yan and Zou, 2013), suggesting triptolide may be an alternative or adjuvant anti-inflammatory agent for treating KD. According to the results of 2 independent clinical studies conducted in mainland China, the treatment of ligustrene (an alkaloid extracted from rhizome of *Ligusticum striatum DC*) in combination with standard KD therapy using AAS, IVIG and anti-blood clot medicine dipyridamole, showed a significantly better improvement in relieving symptoms of increased body temperatures and coronary artery dilation, when compared to the treatment group of Western medicine alone (Luo, 2010; Neng et al., 1996). Tanshinone II-A, a natural compound extracted from *Salvia miltiorrhiza Bunge* (root), was also applied in combination with AAS and IVIG to treat KD. This clinical study confirmed that co-treatment of tanshinone II-A with IVIG and AAS can shorten the time of fever, reduced the level of CRP and facilitated the faster recovery of coronary artery damage when compared to standard IVIG and AAS treatment alone (Zhang et al., 2011).

In addition to single herbal chemicals, reports have also suggested the use of traditional herbal decoctions or formulations for the treatment of KD. For example, “Qing Re Liang Xue” decoction composed of *Salvia miltiorrhiza Bunge, Lonicera japonica Thunb* (flower), *Forsythia suspensa (Thunberg) Vahl* (fruit), *Anemarrhena asphodeloides Bunge* (rhizome), was prescribed with IVIG, AAS, and dipyridamole to reduce platelet count and decrease the serum level of IL-33 and TNF-α to improve the hypercoagulable state of KD patients (Chen et al., 2015), suggesting the effective use of TCMs to alleviate inflammation in KD patients. Similarly, TCMs such as *Salvia miltiorrhiza Bunge*, *Lonicera japonica Thunb*, *Forsythia suspensa (Thunberg) Vahl*, *Cortex Moutan Radicis* (the root bark of *Paonia suffruticosa Andr.*) can help to resume the normal blood platelet level, suppress the activation of platelet, and reduce the incidence of CAL in KD patients (Ruo-Sha and Shu-Juan, 2008). In a cohort study of 109 cases of KD, results have indicated the combined treatment of TCMs containing “Yinqiao-San”, “Qing Ying Tang” or “Radix Ophiopogon soup”, IVIG and AAS, could help to resume the normal level of several physiological markers in KD patients (Qin et al., 2017). In addition, “Bai Hu decoction” can exert anti-pyretic, anti-inflammatory effect and reduce coronary artery

### Table E

List of traditional Chinese medicines or herbal compounds used as adjuvant therapy for treating KD with reported clinical efficacy.

| Single herbal compounds | Source | Pharmacological actions, mechanisms or signaling pathways | References |
|-------------------------|--------|----------------------------------------------------------|------------|
| Resveratrol             | *Vitis vinifera* L. (fruit) | Decreased the level of TNF-α-induced expression and inducible nitric oxide synthase and IL-1β via the activation of autophagy | Huang et al., 2017 |
| Triptolide              | *Tripterygium wilfordii Hook.f.* (root) | Inhibition of oxidative stress and restoration of complex I activity | Abdin and Sarhan, 2014 |
| Tanshinone II-A         | *Salvia miltiorrhiza Bunge* (root) | Lowered the expression level of intercellular cell adhesion molecule-1 and increased the rate of apoptosis of inflammatory cells | Yan and Zou, 2013 |
| Ligustrazine            | *Ligusticum striatum DC* (rhizome) | Anti-inflammatory effect | Zhang et al., 2011 |
| Herbal decoctions       | Herbal composition | Pharmacological actions, mechanisms or signaling pathways | Luo, 2010 and Neng et al., 1996 References |
| Qing Re Liang Xue decoction | *Salvia miltiorrhiza Bunge, Lonicera japonica Thunb* (flower), *Forsythia suspensa (Thunberg) Vahl* (fruit), *Anemarrhena asphodeloides Bunge* (rhizome), etc. | Reduced platelet count and level of serum IL-33 and TNF-α, with improvement in hypercoagulable state | Chen et al., 2015 |
| Yinqiao-San, Qing Ying Tang, Radix Ophiopogon soup etc. | *Mengha, Forsythia suspensa (Thunberg) Vahl*, *Lonicera japonica Thunb*, *Anemarrhena asphodeloides Bunge*, *Cicadae Periostracum* (shell of Cryptopympana pusilulata Fabricius), *Uncaria rhynchophylla*(Miq.) Miq. ex Harv. (hooks and stems) | Anti-inflammatory and protective effect on coronary artery | Qin et al., 2017 |
| Bai Hu decoction        | *Gypsum fibrosum, Anemarrhena asphodeloides Bunge, O. s. sax. japonica, Glycyrrhiza glabra* L. (root) | Exerted anti-pyretic, anti-inflammatory effect and reduced coronary artery inflammation | Wang, 2011 |
| Jie Du Hua Yu decoction | *Forsythia suspensa (Thunberg) Vahl, Lonicera japonica Thunb, Angelica sinensis (Oliv.) Diels* (root), *Cicadae Periostracum, Larncriana* | Anti-inflammatory and reduced coronary artery disease risk | Liu, 2017 |
| Yinqiao-San, Qingwen BaiDu Yin and, Bamboo leaves gypsum soup | *Salvia miltiorrhiza Bunge, Lonicera japonica Thunb, Anemarrhena asphodeloides Bunge, Cicadae Periostracum, Gypsum fibrosum, etc.* | Anti-inflammatory and regulated the immune system | Wang and Feng, 2002 |
inflammation in 32 patients with KD (Wang, 2011). Other reports indicated that 60 cases of KD treated by “Jie Du Hua Yu decoction” in combination with IVIG, showed a shorter symptom duration when compared with other group treated by combination of anti-infective agent (cephalosporin or penicillin) and AAS without IVIG. The clinical parameters such as CRP, erythrocyte sedimentation rate, and recovery rate of coronary artery diameter expansion in TCMs treatment group with IVIG, were improved better than the anti-infective agent and AAS combined treatment group without IVIG (Liu, 2017).

Further clinical studies on the use of herbal decoction in addition to standard AAS and IVIG treatment have confirmed the effectiveness of TCMs as adjuvant therapy to KD. For example, the co-treatment of a herbal decoction containing Gypsum fibrosum, Salvia miltiorrhiza Bunge, Lonicera japonica Thunb. and Forsythia suspensa (Thunberg) Vahl, with AAS and IVIG, can attenuate the symptoms and the level of white blood cell, platelet, CRP and ESR, in a shorter duration than the control group with AAS and IVIG treatment only (Baoshen, 2018; Linlin et al., 2016a; Linlin et al., 2016b). On the other hand, TCMs have also played an important immunomodulatory role in acute phase of KD. For example, “Yinqiao-San”, “Qingwen Baidu Yin” and “Bamboo leaves gypsum soup”, could reduce the inflammatory response during acute phase response and prevent thrombosis by regulating the body immune system in a cohort study of 205 patients of KD (Wang and Feng, 2002). Based on the above clinical observation, TCMs may act as an effective adjunct treatment to KD via shortening the disease duration and reducing the symptoms of the disease with less adverse side effects (Liu, 2017; Wang and Feng, 2002; Wang, 2011).

Based on the above observation, selected herbal chemicals which possess potent anti-inflammatory or immunoregulatory effects are hereby proposed as the potential remedies for the treatment of KD (Fig. B). For example, by interlinking the genetic susceptibility of KD to the traditional clinical applications and modern pharmacological actions of selected natural products, a list of potential herbal candidates for treating KD was proposed as shown in Table F. By targeting the potential KD genes such as TLR4, CASP3 and CD40, several potential effective single components derived from natural plants are suggested. For example, kaempferol derived from Kaempferia galanga L. may work as a novel therapeutic agent for KD via decreasing the expression level of CD40 in the bronchoalveolar lavage fluid cells (Medeiros et al., 2009). Quercetin derived from Fagopyrum tataricum (L.) Gaertn or oaks species can decrease the level of CD40 in cervical carcinoma cells and facilitate cytotoxic T lymphocyte responses (Hill et al., 2005). Similarly, emodin derived from Rheum rhabarbarum L., Rhamnus dahurica Pall (bark), and Reynoutria japonica Houtt (rhizome and root) may also be used for treating KD via its ability in decreasing both CASP3 and TNF-α level, and inhibiting NF-κB activation (Wu et al., 2007). For targeting TLR4 gene, several natural compounds are suggested for future investigation. For example, cryptotanshinone derived from Salvia miltiorrhiza Bunge can decrease the expression of TLR4 in Caco-2 cells stimulated by LPS, suggesting that cryptotanshinone may possess anti-inflammatory property via inhibition of NF-κB signaling pathway and decreased expression of TLR4. Zerumbone derived from Zingiber zerumbet (L.) Smith (rhizome) is a monocyclic sesquiterpenoid, which can

![Fig. B. Suggested possible adjuvant herbal therapies for KD. Schematic diagram showing the proposed use of herbal medicines as adjuvant therapy for KD, by targeting our 3 proposed enriched susceptibility genes to KD. (Red frame: TCMs targeting the gene CASP3; Blue frame: TCMs targeting the gene TLR4; Yellow frame: TCMs targeting the gene CD40), or targeting effectively on the immune and inflammatory system (Green frame: TCMs decoction for anti-inflammatory and immune regulation).](image-url)
reduce the level of pro-inflammatory cytokines such as TNF-α and decrease the upregulated protein level of TLR4 and NF-κB p-p65 for possessing the anti-inflammatory activities (Wang et al., 2019). Leng et al. showed that astragalside IV derived from Astragalus propinquus Schischkin (root) can decrease the expression of TLR4 and NF-κB p65 both in vivo and in vitro, and significantly improved the aortic endothelial function (Leng et al., 2018), suggesting the potential use of herbal chemicals for treating KD.

**Conclusion and perspectives**

Although there were regional and seasonal variation in the epidemiology of KD, the general trend in the incidence rate of KD is increasing worldwide. With the increasing number of cases in KD, the clinical diagnostic guidelines are constantly being updated to classify different types of KD. Although literatures have attributed the pathogenesis of KD to different factors such as regional and ethnic disparities, dietary and environmental factors, infectious agents, immunoregulatory and inflammatory responses, or genetic susceptibility, there is still a lack of a conclusive or integrative summary to confirm the etiology of KD. In fact, KD is classified as a self-limiting acute childhood disease, which is nowadays considered as one of the possible causative reasons for the development of coronary artery disease in adult, therefore, early diagnosis by using high-end technology or identification of specific clinical KD markers deserve our further elucidation. KD is most commonly considered as an immune disease, however, via candidate genes and genome-wide association studies of KD, various genetic factors related to both immune and inflammatory system, which finally contributed to disease susceptibility were discovered. Through bioinformatics analysis, our current study has identified 3 most enriched genes including TLR4, CASP3 and CD40, which are highly correlated to the pathophysiology of KD.

At present, while the combination of IVIG and AAS is the standard therapy adopted in clinical practice worldwide, numerous KD cases were reported to be IVIG resistant. Besides, the possible risk of getting RS after prescription of AAS in children also worth our further identification of adjuvant therapy for KD. In this review, the use of herbal therapies as adjuvant therapy for KD were therefore proposed. While some of the herbal decoctions were suggested for prescription due to their traditional usage in treating KD, herbal chemicals which targeting some of the herbal decoctions were suggested for prescription due to their traditional usage in treating KD, herbal chemicals targeting specific candidates markers of KD could be further evaluated. With the more advanced technology in modern pharmacological research, it is anticipated that novel therapeutic remedies targeting specific clinical markers of KD could be developed for accurate diagnosis and treatment of the disease.
Declarations of Competing Interest
All authors declare no conflict of interest.

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