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Kaempferol – A dietary anticancer molecule with multiple mechanisms of action: Recent trends and advancements

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ABSTRACT

The consumption of diet-based naturally bioactive metabolites is preferred to synthetic material in order to avert health-associated disorders. Among the plant-derived polyphenols, kaempferol (KMF) is considered as a valuable functional food ingredient with a broad range of therapeutic applications such as anti-cancer, antioxidant and anti-inflammatory uses. KMF acts on a range of intracellular as well as extracellular targets involved in the cell signaling pathways that in turn are known to regulate the hallmarks of cancer growth progressions like apoptosis, cell cycle, invasion or metastasis, angiogenesis and inflammation. Importantly, the understanding of mechanisms of action of KMF-mediated therapeutic effects may help the scientific community to design novel strategies for the treatment of dreadful diseases. The current review summarizes the various types of molecular targets of KMF in cancer cells as well as other health-associated disorders. In addition, this review also highlights the absorption, metabolism and epidemiological findings.

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1. Introduction

The interest of scientific community to identify and characterize bioactive constituents from various plant extracts for suitable use in pharmaceutical industry or in composition of functional foods is significantly increasing. Today, it is generally accepted that nutrition plays an important role in the prevention of different chronic diseases and decreasing the risk factors by virtue of its functional ingredients. Among the broad category of plant-derived bioactive compounds, flavonoids are found to possess multiple health benefits. Therefore they are being considered as a medicinally important class of dietary molecules (Ravishankar, Rajora, Greco, & Osborn, 2013). These plant-based secondary metabolites are known to represent a number of structurally diverse classes of polyphenols with potential pharmacological activities, including anticancer, anti-inflammatory, antioxidant, and anti-pathogenic properties (Rajendran et al., 2014; Ravishankar et al., 2013). Indeed, numerous *in vitro* and *in vivo* studies have reported the ability of flavonoids to interfere in different stages of carcinogenesis like migration, invasion, metastasis, and angiogenesis (Ravishankar et al., 2013). Moreover, epidemiological studies have shown that long-term and regular consumption of dietary items rich in flavonoids, such as fruits and vegetables, are associated with the lower risk of malignancy developments (Batra & Sharma, 2013; Kozlowska & Szostak-Wegierek, 2014; Tena et al., 2013). The daily intake of flavonoids among humans is still greatly variable, ranging from about twenty milligrams to virtually one gram (Jaramillo-Carmona et al., 2014). Although, flavonoids are characterized by a common skeleton of diphenyl propane, they can be further subdivided into flavanols, flavonols, flavones, flavanones, isoflavones and anthocyanins based on the peculiarities in their chemical structures (Batra & Sharma, 2013; Kozlowska & Szostak-Wegierek, 2014; Sak, 2014; Tena et al., 2013).

Kaempferol (KMF), a well characterized natural flavonol, is present in 80% of plant-based foods, including broccoli, kale, cabbage, leek, tomato, beans, grapes, strawberries, apples, and tea (Chen & Chen, 2013; Chen et al., 2013; Jaramillo-Carmona et al., 2014; Kim & Choi, 2013; Rajendran et al., 2014). It has been reported that KMF has potential to significantly modulate a variety of signaling pathways that are involved in many adverse clinico-pathological conditions (Batra & Sharma, 2013; Chen & Chen, 2013; Jaramillo-Carmona et al., 2014; Kim & Choi, 2013; Rajendran et al., 2014). In contrast to the standard chemotherapeutic drugs utilized in cancer treatment at present, KMF showed minimal side effects evidenced in the different experiments along with its effective synergistic ability in combination with various synthetic cytotoxic drugs (Chen & Chen, 2013; Chen et al., 2013; Kim & Choi, 2013; Rajendran et al., 2014). However, essential efforts are still needed to uncover its unexplored health benefits. This review highlights the multiple molecular targets of KMF that are involved in a variety of cellular signaling pathways. In addition to this, the review also discusses synergistic studies of KMF with other known therapeutic drugs along with its pharmacokinetics and epidemiological findings.

2. Chemistry and source of kaempferol

Kaempferol (3,5,7-trihydroxy-2-(4-hydroxyphenyl)-4*H*-chromen-4-one) was initially discovered in *Camellia sinensis* (tea tree) and is abundant in different genera of plants such as *Capparis spinosa* (Capers) *and Crocus sativus* (Saffron) (Calderon-Montano, Burgos-Moron, Perez-Guerrero, & Lopez-Lazaro, 2011; Devi et al., 2015; Mercader-Ros et al., 2013, chap. 1). Table 1 summarizes the list of all sort of natural sources of KMF (see Fig. 1).

2.1. Biosynthetic preview

The biosynthetic approach of KMF is known to involve the condensation of cinnamoyl-CoA (1) and malonyl-CoA (2) in the presence of chalcone synthase, a catalytic enzyme, which results in the formation of naringenin-chalcone (3). Chalcone has been considered as the most widely studied precursor for a variety of flavanol synthesis. Further, chalcone isomerase mediates isomerisation reactions and leads to the formation of naringenin (flavanone) (4). In the next step, the hydroxylation is known to occur at C3 position of naringenin by flavanone 3-dioxygenase which leads to the synthesis of dihydrokaempferol (5). In the last step, flavonol synthase mediated exordium of a double bond at the C2–C3 position occurs in the dihydrokaempferol skeleton which results in the formation of KMF (Devi et al., 2015) (Fig. 2). Naturally, KMF is also known to exist in conjugate forms with different sugar molecules such as rutinose, rhamnose, glucose and galactose that cause the formation of glycosidic combinations of KMF, such as astragalin (kaempferol-3-O-glucoside), kaempferol-3-beta-D-galactoside, kaempferol-3-rutinoside. Besides these, other derivatives, such as kaempferol methyl ether, kaempferol dimethyl ether, kaempferol trimethyl ether and kaempferol sulphate have also been noted (Calderon-Montano et al., 2011; Murakami & Tanaka, 1988).

2.2. Chemical synthesis

Chemically, KMF is synthesized by complex reaction having many steps: (a) cross aldol condensation of 2,4,6-trimethoxyacetophenone (6) and 4-methoxybenzaldehyde (7) with KOH, (b) *ortho*-demethylation of 2,4,6,4′- tetramethoxychalcone (8) in the presence of $AlCl_3$, (c) I_2-mediated oxidative cyclization of 2-hydroxy-4,6,4′-trimethoxychalcone (9), (d) methylation of 5-hydroxy-7-methoxy-2-(4-methoxyphenyl)chromen-4-one by Me_2SO_4 (10), (e) oxidative hydroxylation of 5,7-dimethoxy-2-(4-methoxyphenyl)chromen-4-one (11) catalysed by DDO, (f) BBr_3 controlled catalytic demethylation of 3-hydroxy-5,7-dimethoxy-2-(4-methoxyphenyl)chromen-4-one (12) (Lee & Wu, 2001) (Fig. 3A).

Another convenient method for KMF synthesis involves the reaction of ω-benzoyloxyphloracetophenone (13), *p*-(acetyloxy) benzoic anhydride (14), sodium *p*-acetyloxybenzoate (15) in the presence of triethylamine at 160–165 °C for 8 h, followed by mechanical stirring and aqueous KOH treatment that results in the formation of desired product (Ichikawa, Pamukcu, & Bryan, 1982) (Fig. 3B).

3. Therapeutic effects of kaempferol

3.1. Cell cycle arrest and apoptosis by kaempferol

Recent *in vitro* and *in vivo* studies have shown the antiproliferative and proapoptotic activities of KMF against various types of cancers including breast (Azevedo et al., 2015; Kim, Hwang, & Choi, 2016; Liao et al., 2016), ovarian (Luo, Rankin, Li, Depriest, & Chen, 2011), lung (Kuo et al., 2015), pancreas (Zhang, Chen, Li, Chen, & Yao, 2008), esophagus (Yao et al., 2016), stomach (Song et al., 2015), colon (Cho & Park, 2013), prostate (Halimah et al., 2015), bladder (Dang et al., 2015), kidney (Song et al., 2014) and others. Most of these studies demonstrate that the mechanism of KMF is dependent on the inhibition of proliferation of various cancer cells either via cell cycle arrest or induction of apoptosis (Kuo et al., 2015; Liao et al., 2016). KMF-dependent inhibition of cancer proliferation is mediated through arrest of the different phases of cell cycle (Fig. 4) and inhibition of cell cycle transition points

Table 1
An overview about the sources of KMF and its derivatives.

S. no	Derivatives	Plant sources
1.	Kaempferol	*Macrothelypteris torresiana* Ching var. *calvata* Holtt. *Notholaena standleyi* Maxon *Osmunda cinnamomea* L. var. *asiatica* Fern. *Pityrogramma triangularis* Maxon var. *triangularis*
2.	Kaempferol 4′-methyl ether	*Asplenium diplazisorum* Hieron *Notholaena standleyi* Maxon *Pityrogramma triangularis*
3.	Kaempferol 7-methyl ether	*Cheilanthes albomarginata* Clarke
4.	Kaempferol 3-methyl ether	*Notholaena candida* Var. *candida* *N. candida* Hook. Var *Copelandii Tryon* *N. standleyi* Maxon *Pityrogramma triangularis* Maxon var. *triangularis*
5.	Kaempferol 5-methyl ether	*Pityrogramma triangularis* Maxon var. *triangularis*
6.	Kaempferol 3-sulphate	*Adiantum capillus-veneris* L.
7.	Kaempferol 7,4′-dimethyl ether	*Cheilanthes farinosa* KIf C. *grisea* Blanf. C. *kauifussii* Kze.
8.	Kaempferol 3,4′-dimethyl ether	*Notholaena nivea* Desv. *N. standleyi* Maxon *Pityrogramma triangularis* Maxon var. *triangularis*
9.	Kaempferol 3,7-dimethyl ether	*Cheilanthes albomarginata* Clarke C. *farinosa* Kif C. *kaulfussii* Kze. j C. *longissima* C. *rufa* D. Don *Notholaena bryopoda* Maxon *N. cali{ornica* D.C. Eaton (white farina) *N. limitanea* var. *mexicana* Broun
10.	Kaempferol 3,7,4′-trimethyl ether	*Cheilanthes farinosa* Kif. C. *grisea* Blanf. C. *kaulfussii* Kze C. *longissima* *Notholaena hryopoda* Maxon *N. Iimitanea* var. *mexicana* Broun *Pityrogramma triangularis* Maxon var. *triangularis*
11.	Kaempferol 3-O-β-D-glucoside	*Acrophorus nodosus* Pro *Adiantum aethiopicum* L. *A. capillus-veneris* L. *A. cuneatum* Langsd. *A. monochlamys* D.C. Eaton *Alsophila spinulosa* *Christella acuminata* Lev. C. *parasitica* Lev. *Cyathea contaminans* Copel. C. *hancockii* Copel. C. *leichhardtiana* Copel. C. *mertensiana* Copel. C. *podophylla* Hook. *Cystopteris fragilis* Bernh *Davallia divaricata* Bl. *Dennstaedtia scabra* Moore *D. wilfordii* Christ *Hypodematiurn crenatum* Kuhn *H. fauriei* Tagawa *Onoclea sensibilis* L. var. *interrupta* Maxim. *Osumunda cinnamomea* L. var *asiatica* Fern. *Peranema cyatheoides* Don *Phymatodes scolopendria* Ching *Plagiogyria matsumureana* Makino
12.	Kaempferol 3-O-α-D-glucoside	*Athyriumfilix-foemina* Roth
13.	Kaempferol 3-(6-malonyl)-D-glucoside	*Ceterach officinarum* DC
14.	Kaempferol 3-O-(3-O-sulfo)-β-D-glucoside	*Cystopteris fragilis* Bernh.
15.	Kaempferol 3-O-(6-O-sulfo)-β-D-glucoside	*Cystopteris fragilis* Bernh.
16.	Kaempferol 3-O-(6-O-sulfo)-α-D-glucoside	*Athyriumfilix-foemina* Roth
17.	Kaempferol 3-O-β-D-alloside	*Acystopteris japonica* Nakai *Osmunda cinnamomea* L. var. *asiatica* Fern *Wagneriopteris nipponica* Loeve et Loeve

(*continued on next page*)

Table 1 (*continued*)

S. no	Derivatives	Plant sources
18.	Kaempferol 3-O-β-D-galactoside	*Adiantum malesianum* Gatak
		A. monochlamys D. C. Eaton
		Cyathea hancockii Copel
		C. *podophylla* Hook
19.	Kaempferol 3-O-α-D-galactoside	*Adiantum malesianum* Gatak
20.	Kaempferol 3-(6-malonyl)-D-galactoside	*Ceterach officinarum* DC
21.	Kaempferol 3-glucuronide	*Adiantum capillus-veneris* L.
		A. cuneatum Langsd.
22.	Kaempferol 3-O-α-L-rhamnoside	*Alsophila spinulosa* Tryon
		Cyathea contaminans Copel
		C. *hancockii* Copel.
		C. leichhardtiana Copel
		C. *mertensiana* Copel.
		C. *podophylla* Hook.
		Glaphyropteridopsis erubescens Ching
		Pteris ryukyuensis Tagawa
23.	Kaempferol 7-(6-succinyl)-glucoside	*Cyathea contaminans* Copel.
24.	Kaempferol 7-arabinoside	*Alsophila spinulosa* Tryon
		Cyathea hancockii Copel.
		C. *leichhardtiana* Copel.
		C. *mertensiana* Copel
		C. *podophylla* Hook.
25.	Kaempferol 3,7-diglucoside	*Asplenium bulbiferum* Forst.
		A. platyneuron Oakes
26.	Kaempferol 3-glucoside-7-galactoside	*Asplenium bulbiferum* Forst.
27.	Kaempferol 3-O-rhamnoside-7-O-glucoside	*Asplenium bulbiferum* Forst
28.	Kaempferol 3,7-di-O-α-L-rhamnoside	*Asplenium trichomanes* L.
		Onychium contiguum Hope
		Pteris podophylla Sw.
29.	Kaempferol 3-O-rhamnoside-7-O-arabinoside	*Asplenium trichomanes* L
30.	Kaempferol 3-O-α-L-arabinoside-7-O-α-L-rhamnoside	*Woodsia polystichoides* Eaton
31.	Kaempferol 3-O-arabinoside-7-O-rhamnoside	*Asplenium trichomanes* L.
		Polyposdium vulgare L.
32.	Kaempferol 3-O-(3-Oacetyl)-α-L-arabinoside-7-O-α-L-rhamnoside	*Woodsia polystichoides* Eaton
33.	Kaempferol 3,4′-diglucoside	*Cystopteris fragilis* Bemh.
34.	Kaempferol 3-sophoroside	*Alsophila spinulosa* Tryon
		Cyathea contaminans Copel
		C. *leichhardtiana* Copel
		C. *mertensiana* Copel
35.	Kaempferol 3-O-β-gentiobioside	*Asplenium fontanum* Bernh. var. *obovatum*
36.	Kaempferol *3–0-(6*′-sulfo) gentiobioside	*Asplenium fontanum* Bernh. var. *obovatum*
37.	Kaempferol 3-O-β-rutinoside	*Adiantum capillus-veneris* L.
		Cyathea hancockii Copel.
		C. *podophylla* Hook
		Macrothelypteris torresiana Ching var *calvata* Holtt.
		Paesia anfractuosa C. Chr.
		Pteris excelsa Gaud.
		Thelypteris palustris Schott
38.	Kaempferol 3-O-sulforutinoside	*Adiantum capillus-veneris* L.
39.	Kaempferol 3-O-[2-O-(6-O-caffeoyl-β-D-glucosyl)]-β-D-galactoside	*Brainea insignis* J. Sm.
40.	Kaempferol 3-glucosylarabinoside	*Phegopteris polypodioides* Fee
41.	Kaempferol *3-O-(4* or 5-rhamnosyl)-sarabinoside	*Polypodium vulgare* L.
42.	Kaempferol7-rhamnosylglucoside	*Alsophila spinulosa* Tryon
		Cyathea contaminans Copel
		C. *leichhardtiana* Copel
		C. *mertensiana* Copel
43.	Kaempferol 3-O-[3-O-(4-O-caffeoyl-β-D-glucosyl)]-β-D-glucoside-7-O-rhamnoside	*Phyllitis scolopendrium* Newm.
44.	Kaempferol 3-O-sophorotrioside-7-O-glucoside	*Asplenium septentrionale* Hoffm.
45.	Kaempferide 3,7-diglucoside	*Asplenium bulbiferum* Forst
46.	Kaempferide 3-O-glucoside-7-O-rhamnoside	*Asplenium bulbiferum* Forst.
47.	Kaempferide 3-rhamnoside-7-glucoside	*Asplenium bulbiferum* Forst.
48.	Kaempferol 3–0-gentiobioside-7,4′-diglucoside	*Asplenium nidus* L.
49.	Kaempferol 3,4′-dimethyl ether 7-glucoside	*Asplenium platyneuron* Oakes
50	Kaempherol 3,5-dimethyl ether 4′-O-β-D-glucoside	*Colysis wrightii* Ching

Sources adopted from Murakami and Tanaka (1988) and Iwashina & Murai, 2013, chap. 3.
Further details have been cited in Calderon-Montano et al. (2011).

including G0/G1 transition in esophagus squamous cell carcinoma (Yao et al., 2016) or G2/M transition in HT-29 human colon cancer cells (Cho, 2013). KMF additionally inhibits the expression of various cyclins like cyclin D1 and cyclin E in breast cancer cells (Kim et al., 2016), cyclin B1 in gastric cancer cells and renal cell carcinoma (Song et al., 2014, 2015) cyclin D, cyclin E and cyclin A in colon cancer cells (Cho, 2013) and cyclin-dependent kinases like CDK4 and CDK2 (Cho, 2013). KMF treatment has also been known to up-regulate the CDK inhibitors including p21 and p27 (Fig. 4). Furthermore, results of these studies demonstrate that KMF-dependent arrest of G0/G1 or G2/M transition is possibly due to inhibition of epidermal growth factor receptor (EGFR) activity,

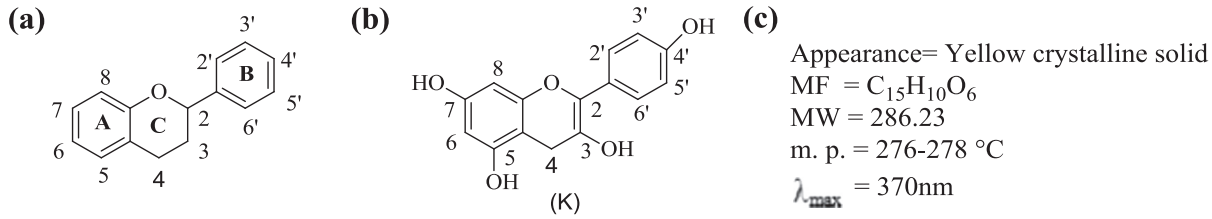

Fig. 1. This figure illustrates the chemical nature and physical characteristics of KMF. (a) The flavonoid diphenyl propane skeleton; (b) Chemical structure of KMF; (c) Physical properties of KMF.

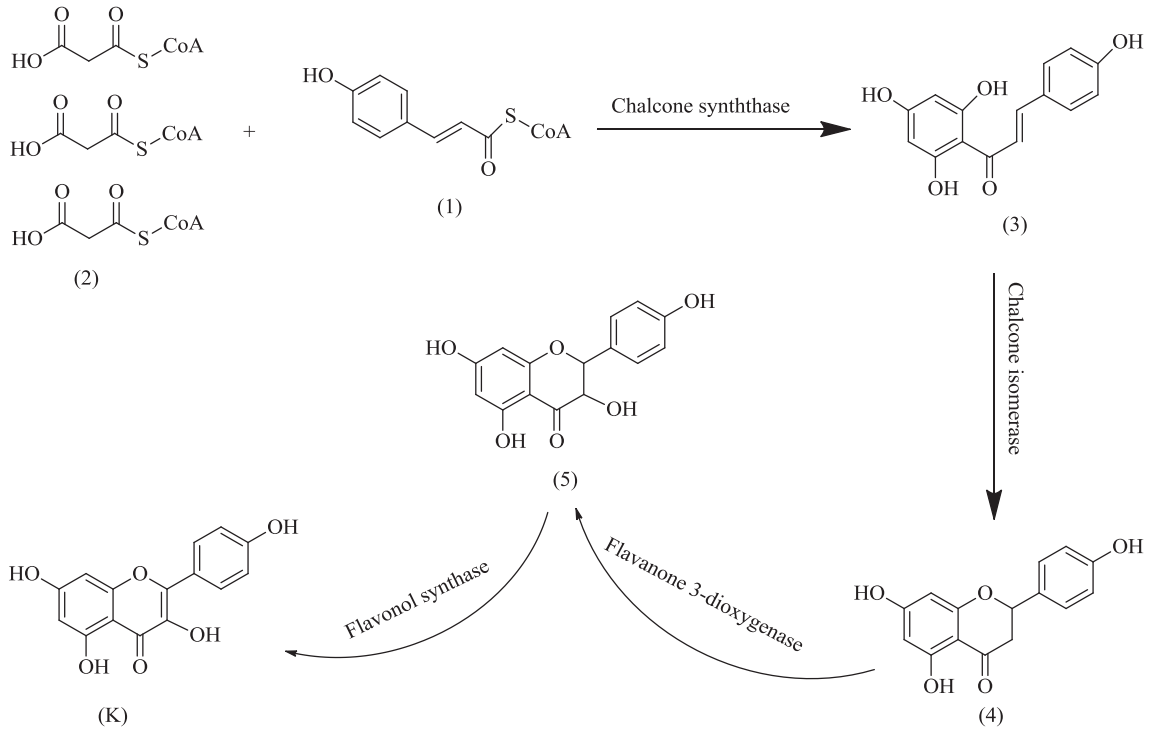

Fig. 2. Biosynthesis of KMF.

hexokinase-2 expression (Yao et al., 2016), inhibition of the activity of estrogen (Kim et al., 2016) or uptake of glucose (Azevedo et al., 2015). Of note, growth factors, hormones, glucose and hexokinases are positive regulators of cell cycle.

A large body of evidence indicates that KMF induces cancer cells apoptosis by activating the apoptosis-related signaling pathways (Fig. 5). Xu, Liu, Li, Wu, and Liu (2008) have indicated mitochondria in human cervical cancer cells (Hela cells) and HEK293 cells (embryonic kidney cells) as the source of KMF-dependent activation of intrinsic apoptotic signaling (Xu et al., 2008). Further, studies by Kang et al. (2009) have substantiated that KMF could cause apoptosis MCF-7 breast cancer cells with estrogen receptor (ER) by activating intrinsic apoptosis signaling pathway and by down-regulation of PLK1 expression (Kang et al., 2009). Similarly, Song et al. (2015) have shown that in gastric cancer cells KMF decreases the expression level of an anti-apoptotic protein Bcl_2 on the mitochondrial membrane and concomitant induction of pro-apoptotic protein Bax release from mitochondria (Song et al., 2015). Very recently, by utilizing a number of cancer cell lines, including human breast carcinoma (MCF-7) cells, human stomach carcinoma (SGC-7901) cells, human cervical carcinoma (Hela) cells and human lung carcinoma (A549) cells Laio et al. have attested that mitochondrial dysfunction is the major reason of KMF-dependent apoptosis induction in these cancer cells (Liao et al., 2016). However, a number of other independent studies claimed that TNF cognate apoptosis-inducing ligand (TRAIL) is related to KMF-dependent apoptosis in cancer cells. Of note, the proinflammatory cytokine TNF-α, and TRAIL are cognate to the activation of extrinsic apoptosis signaling pathway. For example, Yoshida et al. (2008), have shown that KMF-dependent apoptosis in colon cancer cell lines is mediated by inducing TRAIL (Yoshida et al., 2008). Likewise, TRAIL-KMF, mediated apoptosis is the result of suppression of survivin in human glioma cells (Siegelin, Reuss, Habel, Herold-Mende, & von Deimling, 2008). Besides, KMF may also affect and inhibit various pro-survival molecules, i.e. Akt, PI(3)K, ERK 1/2 in the downstream signaling pathways (Kim et al., 2016; Kuo et al., 2015). KMF also suppresses cancer metastasis in osteosarcoma cells (Chen et al., 2013) and induces autophagy (programmed cell survival) in human hepatic cancer cells (Huang et al., 2013). It has been shown that carcinoma cells activate AMP-activated protein kinase-dependent autophagy as the survival response to KMF-mediated energetic impairment (Filomeni et al., 2010). In summary, KMF decreases the number of various cancer cells through a multiprong mechanisms that include the arrest of the cell cycle, activation of proapoptotic proteins, inhibition of anti-apoptotic proteins and by attenuating the phosphorylation and activity of prosurvival proteins (e.g. Akt) and activation of programmed cell survival or autophagy.

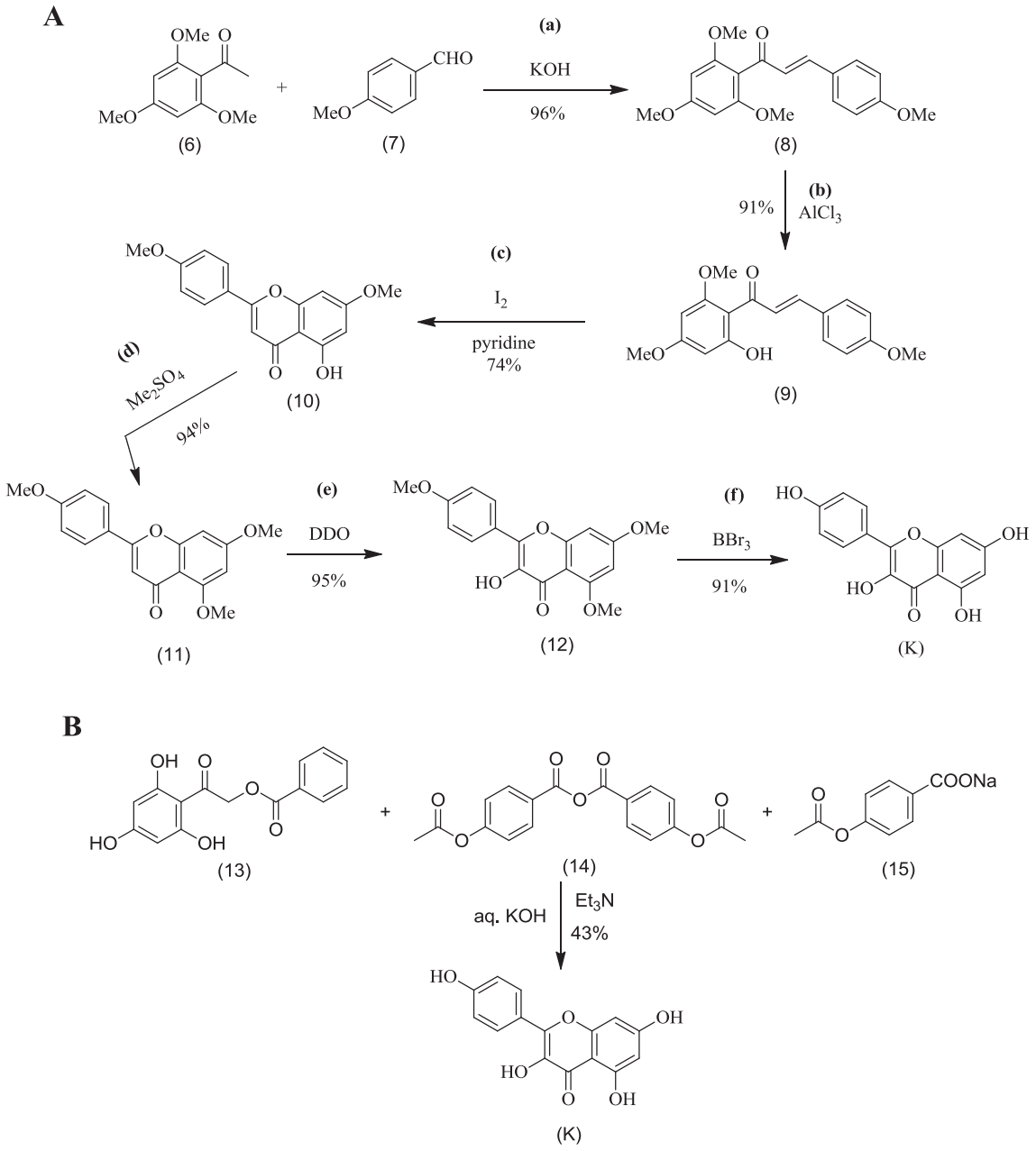

Fig. 3. Schematic representations of methods for chemical synthesis of KMF. (A) Synthesis from 2,4,6-trimethoxyacetophenone; (B) Synthesis from ω-benzoyloxyphloracetophenone.

3.2. Anti-angiogenesis effect of kaempferol

Cancer cells exhibit high metabolic rate to fulfil their energy requirements that in turn is found to be associated with the neovascularization (angiogenesis). A number of studies have reported the involvement of a variety of transcriptional (ERK 1/2, Akt, and MAPK) and growth factors (VEGF and FGF) in the tumour microenvironment for the neovascularization (Kashyap, Rajkumar Mondal, Tuli, Gaurav Kumar, & Sharma, 2016; Kashyap, Sonam Mittal, Sak, Singhal, & Tuli, 2016; Kashyap, Tuli, & Sharma, 2016; Kumar, Mittal, Sak, & Tuli, 2016; Tuli, Sandhu, Sharma, & Gandhi, 2014). These factors are being targeted as therapeutic approach for the cure of cancer in advanced stages (Fig. 6). Treatment of Huh7 cell with KMF under hypoxic (low oxygen tension) condition inhibits the HIF-1α protein through the inactivation of p44/42 MAPK pathways which could be possible ways of cancer inhibition (Mylonis, Lakka, Tsakalof, & Simos, 2010). In a study conducted by Luo et al. (2009) using human ovarian cancer cells, they suggested that KMF can inhibit angiogenesis significantly by altering the VEGF expression through both HIF dependent and independent (ESRRA) pathways (Luo et al., 2009). In context to their previous studies Luo et al. (2012a, 2012b) and Luo, Rankin, Juliano, Jiang, and Chen (2012) further proposed a novel angio-prevention mechanism of KMF via down-regulation of ERK-NFκB-cMyc-p21-VEGF signaling pathway (Luo et al., 2012a, 2012b; Luo, Rankin, et al., 2012). In *in vitro* (HUVECs model) and *in vivo* studies (zebrafish model), Liang et al. (2015) demonstrated the anti-angiogenic effect of KMF via VEGF and FGF angiogenic promoters inactivation that are further known to interact with tyrosine kinase-associated

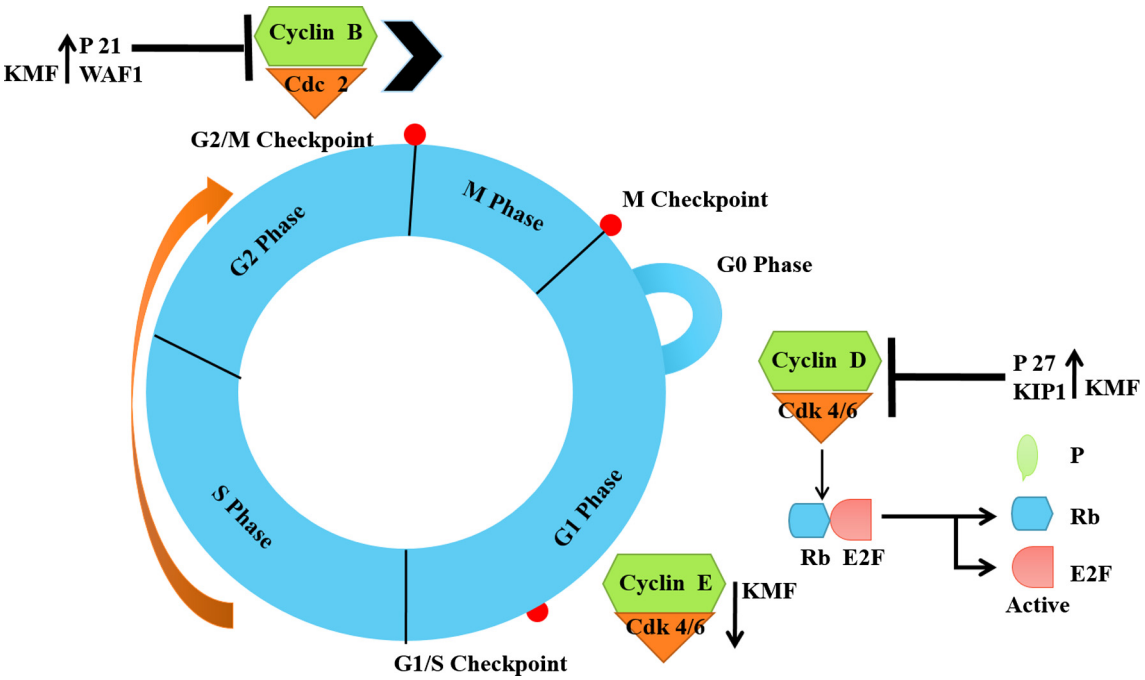

Fig. 4. This figure depicts the cell cycle inhibitory effect of KMF through the regulation of various proteins molecules. KMF inhibits or reduces the expression of cyclin D/cdk 4/6, cyclin E/cdk 4/6, and cyclin B/cdc2 at G_1/S and G_2/M cell cycle check points. It increases the expression of p27, a member of the Kip/Cip family of CKIs which exerts negative regulation of CDK activity at G1/S phase transition. Similarly KMF is also known to enhance the expression level of cyclin-dependent kinase inhibitor $p21^{WAF1/Cip1}$ which promotes the cell cycle arrest in response to various stimuli.

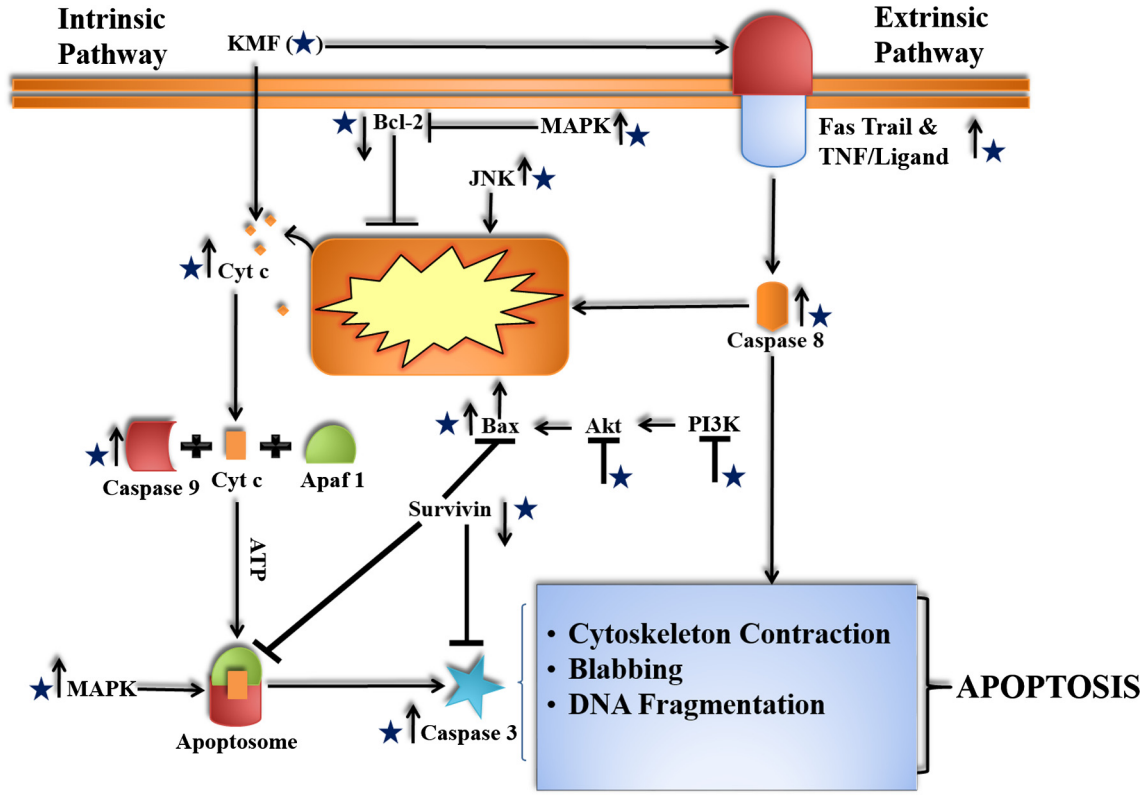

Fig. 5. KMF activates the apoptosis of the tumour cell through both intrinsic and extrinsic pathways. KMF depolarizes the mitochondrial membrane which causes the release of apoptosis mediators (cyt-c) in the cytoplasm. KMF also facilitates the formation of the apoptosome in the cytoplasm to induce apoptosis via caspase 3. It negatively regulates the expression of anti-apoptotic proteins like Bcl2, whereas positively regulate pro-apoptotic protein Bax. The components of extrinsic pathways such as caspase 8 are activated by KMF treatment. Furthermore, the surviving protein has also been down-regulated by the KMF treatment.

angiogenic receptors. Fig. 6 summarizes the various above discussed molecular targets of KMF in the inhibition of cancer angiogenesis and further research is required to explore the remaining details of its mechanisms of action.

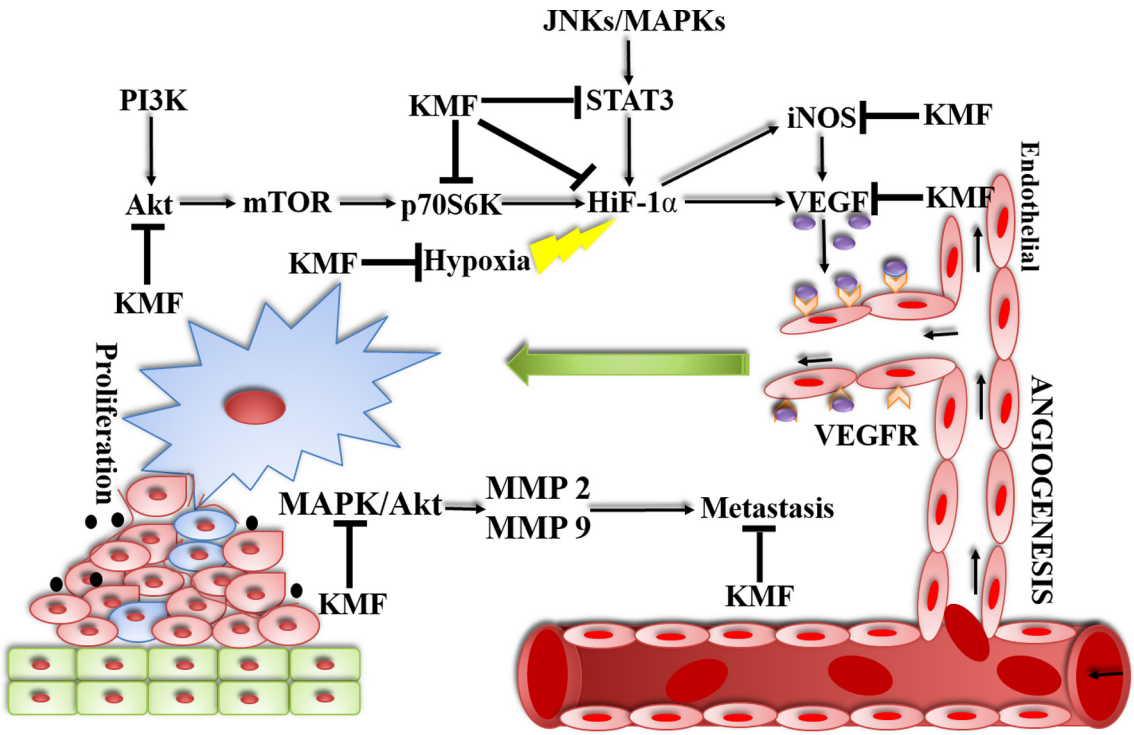

Fig. 6. This figure summarized the KMF-mediated anti-angiogenic and anti-metastatic effects. HIF-1α which initiates neovascularization under hypoxic condition in tumour is found to be inhibited by the KMF. VEGF and its receptor VEGFR mediated activation of endothelia cells are also attenuated in the presence of KMF. Furthermore, KMF inhibits the Akt/mTOR/p07S6K, a well resolved signaling pathways in the neovascularization during the tumour progression. It also inhibits the STAT3 or its phosphorylation that have been required for the signaling cascades via HIF-1α activation. Inflammatory mediators like iNOS which activates the VEGF are noticed as down-regulated by KMF. Moreover KMF also inhibits the MMPs (MMP 2 & 9) via inhibition of MAPK/Akt pathways, both of these enzymes are important for the ECM remodelling during the cancer progression and facilitate the cancer metastasis.

3.3. Anti-metastasis effect of kaempferol

Metastasis is considered as a hallmark of uncontrolled proliferation of the tumour cells at primary site followed by the invasion to the nearby tissue and invasion to the distant organs via bloodstream. The EMT proteins (Epithelial-Mesenchymal-Transitions), such as E-cadherin, vimentin, fibronectin, matrix metalloproteases (MMPs) are known to play a paramount role in the process of metastasis by trailing the cell-cell contacts (Short, Suarez-Zayas, & Gomez, 2016; Tulotta et al., 2016; Zhu, Guo, Wu, & Wei, 2016). Therefore, EMT proteins are considered as promising targets to combat tumour metastasis. The STAT3 is another most widely studied transcription factor associated with cancer metastasis and survival which has been found to be suppressed by KMF treatment in human prostate cancer cells (DU145) (Kwon, Kang, Kang, & Yoon, 2010). In a study by Chen et al. (2013), the anti-metastatic effect of KMF in human osteosarcoma cells (OS) was investigated by inhibiting the DNA binding activity of a transcription factor called activator protein (AP-1) which resulted in reduced expression of MMP-2 & 9 (Chen et al., 2013). Moreover, the other associated molecules, including ERK 1/2 and p38 were also found to be down-regulated under KMF treatment (Fig. 6). Similarly, ERK 1/2-mediated down-regulation of MMPs has observed in KMF-treated human tongue squamous cancer cells (SCC4) (Lin et al., 2013). In another study, KMF suppressed the transforming growth factor-β1 (TGF-β1) induced human non–small cell lung cancer (NSCLC, A549) transition from epithelial-to-mesenchymal (EMT) and migration by abolishing Akt1-mediated Smad3 phosphorylation (Eunji, Park, Choi, Jeon, & Kim, 2015). Correspondingly, Hang, Zhao, Chen, Sun, and Zhang (2015) observed the modulation of EMT-cognate proteins, including E-cadherin and vimentin in KMF-treated non-minuscule lung cancer cells (Hang et al., 2015).

3.4. Anti-inflammatory effect of kaempferol

Inflammation is known to be adopted by the tissues against various endogenous and exogenous pathogens. However, chronic inflammation has been considered to be associated with the progression of various diseases, including cancer, arthritis, and neurodegeneration (Tuli, Chaudhary, Beniwal, & Sharma, 2015; Tuli, Kashyap, Bedi, et al., 2015; Tuli, Kashyap, Sharma, & Sandhu, 2015). KMF has been proven to be a potent inhibitor of pro-inflammatory molecules such as inducible nitric oxide synthase (iNOS), cyclooxygenase (COX), intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) (Kong, Luo, Li, Zhou, & He, 2013a, 2013b; Liu, Xiao, & Fang, 2014). The anti-inflammatory mechanisms of KMF are mainly mediated (Fig. 7) by the down-regulation of several transcription factors, such as NF-κB (nuclear factor kappa B) and STAT that have ability to stimulate the activation of inflammatory molecules (Hamalainen, Nieminen, Vuorela, Heinonen, & Moilanen, 2007). Garcia-Mediavilla et al. (2007) examined the anti-inflammatory potential of KMF in the human hepatocyte-derived cell line and proved that KMF was able to reduce the expression of C-reactive protein (CRP), COX-2, and iNOS via alterations in NF-κB pathway. Osteopontin (OPN), a reactive oxygen species (ROS)-dependent cytokine, which engenders and activates the p38 MAPK and NF-κB signaling, has been found to be down-regulated in aldosterone-induced human umbilical vein endothelial cells (HUVECs) by KMF (Liu et al., 2014). Comparably, KMF treatment in lipopolysaccharide (LPS)-induced macrophages revealed the consequential down-regulation of COX-2, iNOS and TNF-α (tumour necrosis factor-α) both at transcriptional and translational levels via inhibition of NF-κB and AP-1 transcription factor (Kim, Kim, Moh, & Kang, 2015; Kim, Park, et al., 2015). Moreover, the protein

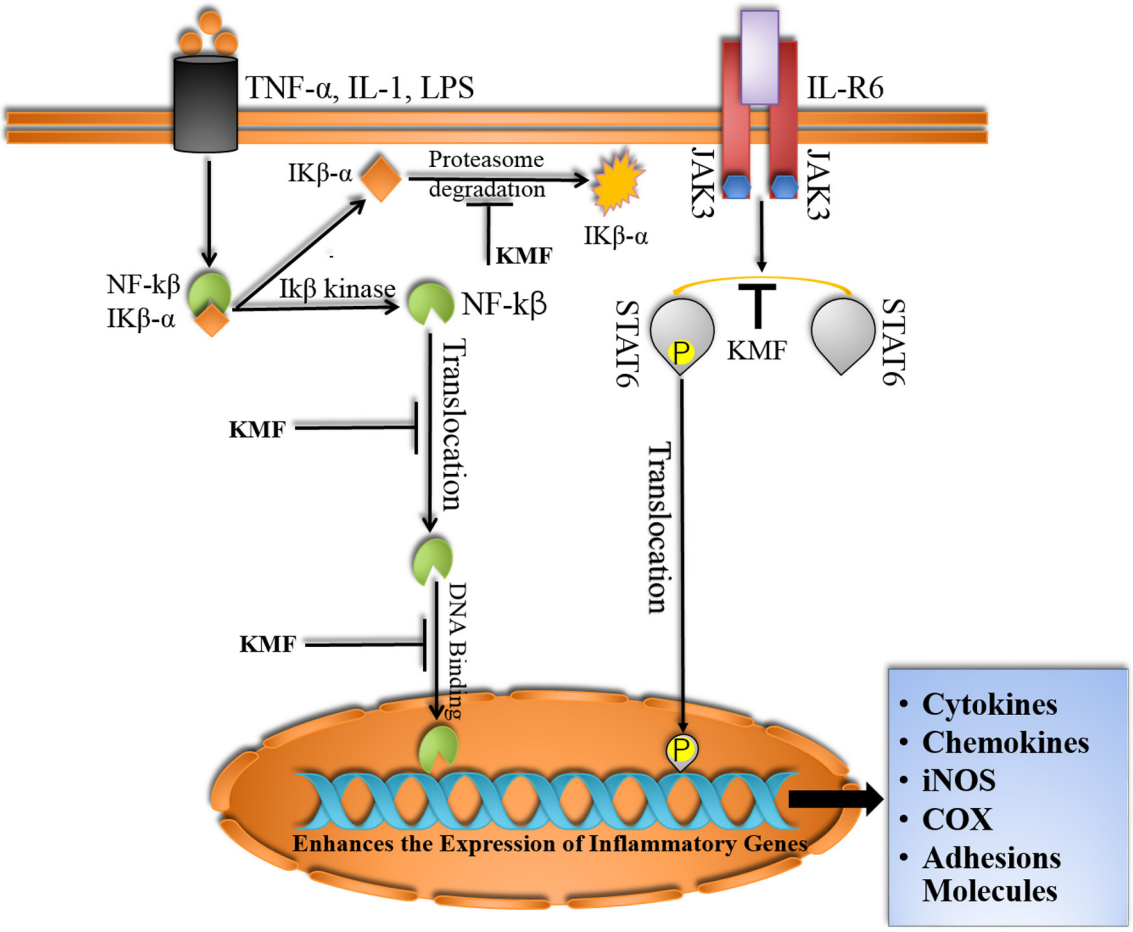

Fig. 7. This figure elaborates the anti-inflammatory activity of KMF. KMF prevents the proteasome degradation of IKβ which forms complex with NF-κβ and stops its translocation in the nucleus. It also directly prevents the translocation of the NF-κβ in the nucleus and its binding to the DNA which otherwise activates the expression of various inflammatory genes. KMF inhibits the phosphorylation of the STAT6 which results in the inhibition of its translocation to nucleus thereby suppressing the activation of various inflammatory genes.

kinase cascade mechanisms governed by Src, Syk, IRAK1, and IRAK4 that are usually involved in the activation of NF-κB and AP-1 transcriptional factors can also be blocked by KMF. The docking studies have substantiated the homogeneous binding energies of KMF as that of MG-132 which is considered to be a potent NF-κB inhibitor (Kadioglu, Nass, Saeed, Schuler, & Efferth, 2015). Therefore, evidences are suggesting that KMF may have great potential as an anti-inflammatory drug and could be introduced for *in vivo* trial.

3.5. Antioxidant properties of kaempferol

Reactive Oxygen Species (ROS) generated by enzymatic reactions during metabolism are the major source of harmful oxidative stress (Adegoke & Forbes, 2015; Hazra, Sarma, & Sanyal, 2004). Although human body has antioxidant enzymes as a defenses mechanism that constantly neutralizes the ROS, the excess concentrations of ROS become fatal and cause cellular dysfunction, oxygen toxicity, senescent, stroke, autoimmune diseases, cancer, Parkinson's disease, infection and arteriosclerosis (Adegoke & Forbes, 2015; Melo et al., 2015). Studies have been performed using various funtional foods with antioxidant agents that may be availed to dispense ROS (Gao, Yang, & Xu, 1999; Kim et al., 2003). These results showed that flavonols could be effective secondary metabolites against oxidative stress (Yoshida et al., 2008). KMF directly scavenges peroxynitrite (reactive nitrogen species) and hydroxyl radicals at low concentration whereas at high concentrations it enhances the expression of antioxidant enzymes (Calderon-Montano et al., 2011). The proposed mechanisms of action of KMF as a potent antioxidant have been reported to be associated with its up-regulatory effect on antioxidant response elements (ARE)-mediated antioxidative enzymes (Fig. 8), such as heme oxygenase, catalase and superoxide dismutases (SODs) under the control of Nuclear factor (erythroid-derived 2)-like 2 (Nrf2) signaling pathways (Saw et al., 2014). KMF can also be utilized in the inhibition of platelet aggregation and LDL (Low-Density Lipoprotein) oxidative susceptibility (Kowalski, Samojedny, Paul, Pietsz, & Wilczok, 2005). Choe et al. (2012) extracted and purified KMF from the roots of *Rhodiola sachalinensis* and anticipated its antioxidant potential (Choe et al., 2012). Similarly, Wahab et al. (2014) extracted KMF from the beans of *Cassia alata* to study its antioxidant properties. KMF has additionally been found to bulwark myocardial ischemia/reperfusion (I/R) injury in rats by incrementing the calibers of SOD and decrementing the activity of P-GSK-3β (Zhou et al., 2015). In a study, utilizing 1,2-dimethyl hydrazine induced male Wistar rats, Nirmala and Ramanathan (2011) investigated that KMF treatment not only lowered down the erythrocyte lysate and thiobarbituric acid reactive substances (TBARS) but additionally up-regulated the antioxidant enzymes, including catalase, SOD, and glutathione peroxidase (Gpx) levels (Nirmala & Ramanathan, 2011). Likewise, hepatoprotective effect of KMF glycosides has been investigated against

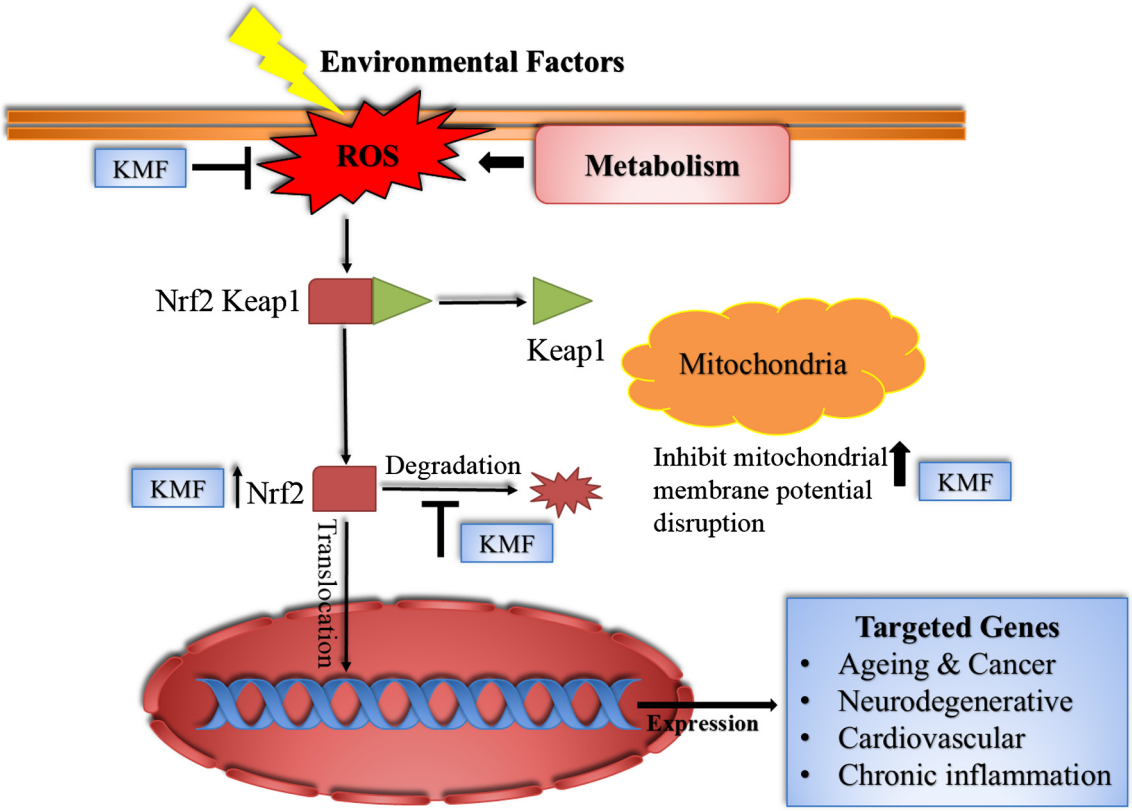

Fig. 8. Schematic representations of anti-oxidant mechanisms of action of KMF. KMF positively regulates the Nrf2 expression, a crucial molecules known for anti-oxidant function. Mechanistically, KMF dissociates the Nrf2 from its repressor Keap1, prevent its degradation and facilitates its translocation to nucleus. KMF also stabilize the mitochondrial membrane potential and helps to reduce the ROS release in the cytoplasm.

carbon tetrachloride-induced liver injuries in mice by uplifting the oxidative stress scavenging potential (Wang, Sun, Jiang, Xie, & Zhang, 2015; Wang, Tang, & Zhang, 2015). In osteoblast-like MC3T3-E1 cells, KMF inverted the antimycin A (AMA)-induced toxicity by averting the disruption of mitochondrial membrane potential and accumulation of intracellular calcium ions and ROS via P(I) 3K-Akt-CREB pathway (Choi, 2011).

3.6. Synergistic and other therapeutic effects of kaempferol

Data about phytochemicals have proved that the synergistic properties of different flavonoids may not only be utilized to enhance the potential of chemotherapeutic drugs, but also to reduce the ineluctable side effects (Kumar et al., 2015; Tuli, Kumar, Sandhu, Sharma, & Kashyap, 2015; Tuli, Sharma, Sandhu, & Kashyap, 2013). In this scenario, KMF could act as a promising molecule to boost the therapeutic potential of the chemotherapy by refining the pharmacokinetics as well as by subsisting side effects of the therapy. A coalescence of quercetin, kaempferol and naringenin was found to be significantly more efficacious antiproliferative agent against mouse liver cancer cells Hepa-1c1c7 and human prostate cancer cells LNCaP (Campbell, King, Harmston, Lila, & Erdman, 2006). In a study utilizing male SD rat models, Xu, Yang, Zheng, Zhu, and Zhu (2006) observed that KMF improves the pharmacokinetics of nifedipine by reducing the drug metabolic processes (Xu et al., 2006). Similarly, the pharmacokinetics of tamoxifen has also been found to be altered by KMF via inhibition of drug metabolizing enzymes, including CYP3A (Piao, Shin, & Choi, 2008). Besides inhibiting the activity of phase I CYPs enzymes, KMF additionally works as an inhibitor of multidrug resistance protein 1 (MDR1) or P-glycoproteins when co-administrated with etoposide and quercetin in rats and in human leukemic cells K562/A, respectively (Li, Li, & Choi, 2009; Yanqiu et al., 2013). The neuroprotective effects of quercetin, KMF and biapigenin have been investigated against kainate and *N*-methyl-*D*-aspartate-induced neuronal cell death by Silva, Oliveira, Dias, and Malva (2008). Utilizing ovarian cancer cell lines, Luo et al. investigated that KMF intensified the apoptotic effect of cisplatin by significantly down-regulating c-myc gene expression (Luo, Daddysman, Rankin, Jiang, & Chen, 2010). Thus, drug combinations could co-act and potentiate the control of intricate biological disorders. Besides governing these promising pharmacological effects, KMF has additionally been known to promote other organ protective effects as summarized in Table 2.

4. Absorption, metabolism and bioavailability of kaempferol

Although countless physiologically important functions of KMF have been described, poor bioavailability restricts its further clinical applications.

Flavonols are naturally dynamic polyphenolic compounds that are found in plants and plant-inferred nourishments of human diet. Their absorption as well as bioavailability in the blood is found to influence their ability to impact the cellular health. After intake, flavonoids undergo to metabolic processes as results of which they are enzymatically conjugated with sulphate, methyl or glycuronyl moieties.

Different methodologies, including estimation of dietary intake, determination of plasma or urinary level, have been used to study the absorption and bioavailability potential of flavonoids. In the USA and Netherlands, KMF gives an important contribution to the daily consumption of flavonoids (25–33%), with a mean intake

Table 2
Summary of a variety of therapeutic effects of kaempferol.

S. no.	Property	Mechanism	Model	Dose	References
1	Cardio-protection	Increase SOD, P-GSK-3β, GSH/GSSG ratio, improve the recovery of LVDP, dp/dtmax, and decrease cleaved caspase-3, cyt-C, CK, LDH, MDA, TNF-α	Sprague-Dawley rat	15 mmol/L	Zhou et al. (2015)
		Decrease TNF-α, IL-6, and NF-$\kappa\beta$, inhibit JNK and p38 protein, reduce expression of Bax and Caspase-3, increase Bcl-2 and activate ERK1/ERK2, prosurvival kinase	Wistar rat	20 mg/kg	Kapil et al. (2016)
		Activate BMP signaling pathway, induces miR-21 expression, downregulates DOCK4, 5, and 7 and antagonizes the PDGF-mediated pro-migratory effect	VSMC cells	50 μM	Kim et al. (2015)
		Inhibit intrinsic and extrinsic pathways of apoptosis, and regulate SIRT1 expression	Rat	15 mM	Guo et al. (2015)
		Inhibit CaMKII oxidization	Mice	15 mM	Minae and Minsuk (2015)
		Decrease TNF-α, IL-1β, MDA, E-sel, ICAM-1, VCAM-1 and MCP-1, and increase serum SOD	Male New Zealand white rabbit	150 mg/kg and 30 mg/kg	Kong, Luo, Li, Zhou, and He (2013a, 2013b)
2	Pulmonary and Asthma-protection	Inhibit IRE1α- TRAF2-JNK activation	BALB/c mice	10 mg/kg	Sin et al. (2015)
		Modulate Syk-PLC, and PKC-ERK-cPLA2-COX2 signaling in antigen-exposed mast cells	Rat	20 mg/kg	Daekeun et al. (2015)
		Modulate Tyk2-STAT1/3 signaling and increase SOD	BEAS-2B cells and BALB/c mice	$\leqslant$20 μM	Gong et al. (2013)
		Inhibit alveolar wall thickness, alveolar hemorrhage and leukocytes infiltration, reduced MPO activity, inactivate MAPKs, and NF-kβ signaling pathways	Male BALB/c mice	100 mg/kg	Chen et al. (2012)
3	Diabetic-protection	Modulate AMPK activity, Glut4 expression, and improve islet β-cell mass	Mice	0.05%	Hana et al. (2015)
		Ameliorate hyperglycemia by acting as partial agonists of PPARγ	3T3-L1 preadipocytes	10 μM	Yun et al. (2010)
		Increase the activity of Sp1 through stimulation of Sp1 phosphorylation by ERK1/2 and subsequent induction of LDLR expression and activity	HepG2 cells	100 μM	Ochiai et al. (2016)
		Inhibit the phosphorylation of insulin IRS-1, Ikβ kinase α, and Ikβ kinase β	Rat	50 or 150 mg/kg	Luo et al. (2015)
		Decrease activity of total ATPases, Na(+)/K(+)-ATPase, Ca(2+)-ATPase, and Mg(2+)-ATPase in erythrocytes and tissues	Wistar rat	100 mg/kg BW	Al, Veeramani, Alsaif, and Chandramohan (2015)
		Inhibit α-glucosidase	–	1.16 ± 0.04 × 10(-5) mol L^{-1}	Peng, Zhang, Liao, and Gong (2015)
4	Osteo-protection	Inhibit bone marrow adipogenesis	Sprague–Dawley rat	1 mg/kg	Ritu et al. (2008)
		Downregulate ER, and activate ERK	MG-63 human osteoblasts	50 mM	Christophe, Jean, Cécile, Alice, and Michel (2004)
		Stimulate Krt-14 protein	Osteoblast cells	5 μM	Khedgikar et al. (2016)
		Enhance the expression of chondrogenic marker genes, such as collagen type I, collagen type X, OCN, Runx 2, Sox 9, induced ERK, and increase expression of BMP-2	ATDC5 cells	5 μM	Nepal, Li, Cho, Park, and Soh (2013)
5	Neuro-protection	Inhibit STAT 3, NF-kβ activation, interleukin 1β, intercellular adhesion molecule 1, MMP 9, iNOS, myeloperoxidase, and TNF-α	Male Sprague-Dawley rat	10.0 mg/kg and 7.5 mg/kg	Lu et al. (2013)
		Inhibit MCP-1 production	Macrophage cell line J.774.2	30 μM	Jan, Arkadiusz, Monika, Grayna, and Tadeusz (2005)
		Autophagic enhancement through LC3-II increase	Rat	30 μM	Giuseppe et al. (2012)
		Inhibit expression of OX-42, glial fibrillary acidic protein, phosphorylated STAT3, NF-$\kappa\beta$ p65, the nuclear content of NF-$\kappa\beta$ p65, inhibit expression of TNF-α, IL-1β, intercellular adhesion molecule 1, MMP 9, iNOS, and myeloperoxidase	Sprague-Dawley rats	–	Yu et al. (2013)
		Improve motor coordination, raise striatal dopamine, increase SOD and GSH-PX activity, and reduce content of MDA	Mice	–	Li and Pu (2011)
		Down-regulate TLR4, NF-kβ, p38 MAPK, JNK and AKT	Microglial BV2 cells	10–100 mM	Park, Sapkota, Kim, Kim, and Kim (2011)
6	Anti-depressant	Modulate POMC mRNA or plasma β-endorphin	Male ICR mice, Male albino mice, and Wistar rat	500 μl/25 g, 100 and 200 mg/kg in mice and 50 mg/kg in rat	Soo, Yun, Pyung, Jin, and Hong (2010) and Hossein, Vahidehsadat, and Farzin (2007)
7	Hepato-protection	Inhibit ENRD	Rat hepatocytes	0.1, 1, 10 μM/L	Zhang et al. (2006a, 2006b)
		Activate LXR-β and suppresses SREBP-1	Mice	150 mg/day/kg	Hoang et al. (2015)
		Attenuate the activity and expression of CYP2E1	Mice	13.23 μM/mL	Wang, Sun, et al. (2015) and Wang, Tang et al. (2015)
		Decrease expressions of TGF-β1 and Smad 2/3, and increasing the expression of Smad 7	BALB/c	5, 10, 15, 20 mg/kg	Cai, Zhao, Li, and Zhang (2014)
8	Arthritis-protection	Inhibit RANKL-mediated phosphorylation of ERK 1/2, p38, JNK MAP kinases, and expressions of c-Fos and NFATc1	Mice	100 μM	Lee, Lee, Sung, and Yoo (2014)
		Inhibit expression of MMP-1, MMP-3, COX-2, PGE2, phosphorylation of ERK-1/2, p38, JNK, and activation of NF-$\kappa\beta$	RASF cells	100 μM	Yoon et al. (2013)

(*continued on next page*)

Table 2 (*continued*)

S. no.	Property	Mechanism	Model	Dose	References
9	UV-protection	Reduced CREB, c-Fos, histone H 3, and inhibit RSK2 and MSK1	Human squamous cell carcinoma	2.5 mg	Ke et al. (2014)
		Suppresses COX-2 expression by blocking Src kinase activity	JB6 P + mouse epidermal cells	20 or 40 μM	Kyung et al. (2010)
10	Ovary-protection	Induce expression of PR regulated transcriptional targets (Hand2 and Areg) without PR degradation	Rat	20 μM	Toh et al. (2014)
11	Immunosuppressant	Increase CD4 + FoxP3 + Tregs, suppress DC maturation and their IL-6 expression	Mice	0.1 mg	Zeng et al. (2015)
12	Anti-parasitic	Entamoeba histolytica trophozoites, through deregulation of cytoskeleton-related protein	–	27.7 μM	Bolaños et al. (2015)
		Chloroquine-resistant *P. falciparum*	*P. falciparum* strain, K-1	106 μM	Melisa et al. (2014)
13	Anti-viral effect	Inactivate virus by binding with JEV fsRNA	Virus-infected BHK21 cells	25 mM	Ting et al. (2012)
		Anti-HIV-1 reverse transcriptase	PBMCs	100, 50, 25 and 10 μg/ml	Behbahani, Sayedipour, Pourazar, and Shanehsazzadeh (2010)
		Coronavirus by targeting 3a channel	Xenopus oocyte	20 μM	Schwarz et al. (2014)
		Enterovirus 71 (EV71) by regulating IRES associated *trans*-acting factors	EV71 isolate	35 μM	Tsai et al. (2011)
14	Anti-fungal	Reversion of resistant *C. albicans* by suppression of CDR1, CDR2, and MDR1	*C. albicans* z2003	128–256 μg/mL	Shao, Zhang, Wang, Li, and Wang (2015)

Foot Note - SOD (Superoxide dismutase), P-GSK-3β (Glycogen Synthase Kinase 3), LVDP (Left Ventricular Developed Pressure), cyt-C (cytochrome-c), CK (Creatine kinase), LDH (Lactate dehydrogenase), MDA (Malondialdehyde), TNF-α (Tumour necrosis factor-α), IL-6 (Interleukin 6), NF-$\kappa\beta$ (nuclear factor kappa-light-chain-enhancer of activated B cells), JNK (c-Jun N-terminal kinases), Bax (Bcl-2-associated X protein), Bcl-2 (B-cell lymphoma 2), Dock4, (Dedicator of cytokinesis 4), SIRT 1 (Sirtuin 1), PDGF (Platelet-derived growth factor), CaM kinase II (Ca2+/calmodulin-dependent protein kinase II), IL1β (Interleukin 1 beta), ICAM-1 (Intercellular Adhesion Molecule 1), VCAM-1 (Vascular cell adhesion protein 1), MCP-1 (Monocyte Chemoattractant Protein-1), COX-2 (Cyclooxygenase-2), STAT1/3 (Signal transducer and activator of transcription 3), MPO (myeloperoxidase), MAPK (Mitogen-activated protein kinase), AMPK (AMP-activated protein kinase), PPARγ (Peroxisome proliferator-activated receptor), Sp1 (specificity protein 1), ERK (Extracellular signal–regulated kinases), Krt-14 (Keratin 14), BMP2(Bone morphogenetic protein 2), MMP-9 (Matrix metallopeptidase 9), iNOS (Inducible nitric oxide synthase), GSH-PX (Glutathione peroxidase), TLR4 (Toll-like receptor 4), AKT (Protein kinase B), LXR-β (Liver X receptor-β), SREBP-1 (Sterol regulatory element-binding proteins), CYP2E1 (Cytochrome P450 2E1), TGF-β1 (Transforming growth factor beta 1), NFATc1 (nuclear factor of activated T-cells 1), CREB (cAMP response element-binding protein).

of 6–10 mg/day (Hertog, Hollman, Katan, & Kromhout, 1993; Sampson, Rimm, Hollman, De Vries, & Katan, 2002). Though, studies have been done concerning the assimilation of other flavonoids, like quercetin, the data on the bioavailability of KMF has still remained to elucidate. DeVries et al. (1998), conducted a 7-days study by utilizing tea and onions-based diet in a group of volunteers to quantify the concentrations of KMF in plasma and urine (DeVries et al., 1998). Their results revealed that KMF was excreted in about 2.5% of its consumed quantity which was higher than for quercetin (0.5%) after 4 h of dose ingestion. Similarly, using healthy humans as subject models, DuPont, Day, Bennett, Mellon, and Kroon (2004) have also reported the similar concentration (0.05 mM) of KMF in plasma after 4 h of intake of endive-based diet, containing up to 246 mg of KMF per kg (DuPont et al., 2004). In another study, researchers observed the KMF excrete about 0.9% of the total consumed flavonoids from broccoli (Nielsen, Kall, Justesen, Schou, & Dragsted, 1997). Furthermore, the absorption rate of KMF from small intestine mainly depends on the microbial hydrolysis of β-glucuronide before aglycone uptake. Rowland, Wiseman, Sanders, Adlercreutz, and Bowey (2000), reported that variation in the gut microflora population alters the absorption rate of KMF by modulating the process of hydrolysis of conjugates and alterations in aglycone ring (Rowland et al., 2000). Chromatographic studies revealed the presence of early absorption peak preferentially due to the absorption of kaempferol-3-glucoside. Nemeth et al. (2003), investigated that kaempferol-3-glucoside is the most preferred substrate for lactase-phlorizin hydrolase, as compared to kaempferol-3-(6-malonyl)-glu coside and kaempferol-3-glucuronide (Nemeth et al., 2003). Being hydrophilic in nature, kaempferol-3-glucuronide is found to be absorbed directly from the small intestine. KMF glucosides are preferentially absorbed via mechanisms of active transport and deglycosylation processes as reported for quercetin absorption (Day, Gee, DuPont, Johnson, & Williamson, 2003; Day et al., 2000; Gee et al., 2000; Nemeth et al., 2003). Hydroxylation is a phase I cytochrome P450 dependent enzymatic activity that is known to be involved in the metabolism of KMF. In a study, Nielsen, Breinholt, Justesen, Cornett, and Dragsted (1998), investigated the hydroxylation capability of microsomes toward flavonols and flavones (Nielsen et al., 1998). Like quercetin, KMF may also be subjected to basic phase II metabolic conjugation in accumulation with glucuronide or sulphate (Day et al., 2001). It is essential to identify KMF metabolites to know the various circulating forms of this moiety. DuPont et al. (2004), has observed the conjugated form of KMF metabolite i.e. kaempferol-3-glucuronide (55–80%) in the circulating plasma (DuPont et al., 2004). Another form of metabolite subsists as kaempferol-7-sulphate which could be due to the action of human hepatocytes (Day et al., 2001). These evidences have suggested the lesser bioavailability of KMF in the bloodstream, which needs to be improved with the aim to utilize the full therapeutic potential of KMF. Using *G. biloba* extract-phospholipid complexes (GBP) of KMF, Chen et al. (2010), have shown the increase in oral bioavailability of flavonoids including quercetin and KMF in a rat model (Chen et al., 2010). Similarly, Wang, Sun, et al. (2015) and Wang, Tang, et al. (2015), investigated that phospholipid complex (TFH-PC) of KMF may not only increase the bioavailability (172%) but also increase the solubility (22.0 folds) in comparison to total intake of flavonoids (Wang, Sun, et al., 2015; Wang, Tang, et al., 2015). Another approach to improve the bioavailability of the therapeutically active flavonols is to explore the effect of the supplemented food matrix ingredients. So far, very limited data are reported about the effect of food ingredients on absorption and bioavailability of KMF. It has been found that the total absorption and bioavailability of flavonoids are

associated with the composition of carbohydrate based food matrix. Rodriguez-Mateos, Oruna-Concha, Kwik-Uribe, Vidal, and Spencer (2012), demonstrated that the maltitol and sucrose were found to increase and decrease the absorption of flavonoids by altering the activity of catechol-O-methyltransferase (Rodriguez-Mateos et al., 2012). Also, the methylation of flavonoids, such as genistein and KMF, appeared to modulate the metabolism as well as transportation of these wonderful molecules. Cao, Jing, Wu, and Shi (2013), indicated that the methylation of KMF not only enhances its transporting ability but also increases its hydrophobicity which further assists in the absorption, bioavailability, and binding affinity to both HSA (human serum albumin) and ovalbumin (Cao et al., 2013). Furthermore, route of administration and nanotechnology-mediated implementations in the drug delivery may also ameliorate the bioavailability of KMF. In 2009, Barve et al. reported that the half-life of KMF was 3–4 h and 1–2 h, respectively, after intravenous (10 and 25 mg/kg) and oral (100 and 250 mg/kg) dosages of KMF in male SD (Sprague-Dawley) rats (Barve et al., 2009). In a study, Luo et al. (2012a, 2012b) and Luo, Rankin, et al. (2012), observed that encapsulated poly (ethylene oxide)-poly(propylene oxide)-poly(ethylene oxide) (PEO-PPO-PEO) and poly(DL-lactic acid-co-glycolic acid) drug dosages were found to be more efficacious than KMF alone (Luo et al., 2012a, 2012b; Luo, Rankin, et al., 2012). Similarly, nano-suspension of KMF was found to improve its bioavailability as well as solubility by increasing the Cmax and Area under the curve ($AUC_{0-\infty}$) value (Qian et al., 2016). Therefore, the data confirmed the significance of bioavailability and solubility of flavonoids to exert their bioactivity and indicated that improving these important pharmacokinetic parameters may probably further enhance the biological efficacy and potential physiological capacity of KMF.

5. Epidemiological findings of studies with kaempferol-rich foods

Epidemiological studies about association between kaempferol-rich foods intake and decrease in risk of certain types of cancer have shown the variable results depending on several factors, including population type, sample size, food composition, databases used, and other concurrent lifestyle determinants.

No association between consumption of KMF and total invasive cancer risk was found among middle-aged and older women in the Women's Health Study (Wang et al., 2009). However, among 66,940 women included in the Nurses' Health Study, Gates et al. observed a significant (40%) reduction in ovarian cancer incidence for the highest versus the lowest quintile of KMF intake (Gates et al., 2007). On the other hand, a large-scale case-control study showed non-significant (21%) reduction in the incidence of ovarian cancer among women who were at highest quintile of KMF intake (Gates et al., 2009). Similarly, a non-significant (27%) decrease in ovarian cancer risk was noted to be associated with a high KMF intake in a rather small case-control study (124 ovarian cancer cases and 696 population-based controls) conducted in the western New York (McCann, Freudenheim, Marshall, & Graham, 2003).

In addition, there was no evidence showing a relationship between KMF intake and breast cancer risk described in the Nurses Health Study II (Adebamowo et al., 2005), whereas a low consumption of KMF was significantly associated with decreased risk of estrogen receptor (ER) negative-neoplasias compared to ER-positive tumour among premenopausal women (Touillaud et al., 2005). An inverse association of KMF intake with advanced stage (stage III/IV or stage IV, but not non-advanced) prostate cancer in the Netherlands Cohort Study was also described (Geybels et al., 2013). Although there was no remarkable relationships between high KMF intake and colorectal cancer risk among women from the Nurses' Health Study and men from the Health Professionals Follow-Up Study (Lin et al., 2006), a statistically significant reduction in the risk of advanced adenoma recurrence was observed in Polyp Prevention Trial (Bobe, Sansbury, et al., 2008). Furthermore, consumption of higher dose of KMF was found to be protective against gastric cancer in a case-control study conducted in the Spain (Garcia-Closas, Gonzalez, Agudo, & Riboli, 1999). KMF intake was also significantly associated with decreased risk of pancreatic cancer among current smokers (but not among never or former smokers) in the large Multiethnic Cohort Study with participants from Hawaii and California (Nothlings, Murphy, Wilkens, Henderson, & Kolonel, 2007) and among male smokers who were not consuming supplements of vitamin E or β-carotene in the α-Tocopherol, β-Carotene Cancer Prevention Study (Bobe, Weinstein, et al., 2008). Moreover, high intakes of KMF were inversely associated with the development of lung tumour in a case-control study carried out in Los Angeles County, manifesting still only among tobacco smokers and not among non-smokers (Cui et al., 2008). The data of a case-control study of lung cancer in women in Spain exhibited a non-significant association for the highest vs. lowest tertile intake of KMF (Garcia-Closas, Agudo, Gonzalez, & Riboli, 1998).

Consequently, in the above-presented findings, consuming KMF rich diet may be related to lower cancer risk which could be feasible in specific tumour types and in certain populations. More epidemiological studies with larger cohorts are required to further investigate the potential role of kaempferol-rich foodstuffs in prevention of chronic diseases, such as cancer.

6. Conclusion and future perspectives

Functional foods have always been known to upgrade health benefits due to their broad spectrum of biological functions and interactions. Evidences have suggested the salutary effects of dietary KMF in plummeting the peril of lethal diseases, such as cancer. Current chemotherapeutic agents are known to pose serious health risks which could be solved by utilizing natural bioactive metabolites like KMF. However, the scientific community should always endeavour to ameliorate the potency of such wondrous molecules. As the structure of KMF revealed the availability of electron donor atoms, such as oxygen which can make the co-ordinate bond with metal atoms and resulting metal complexes of KMF may further boost its biological activity (Kashyap, Rajkumar Mondal, et al., 2016; Kashyap, Sonam Mittal, et al., 2016; Tuli, Sandhu, & Sharma, 2014). Computational implements like QSAR models can be acclimated to explore the unknown molecular interactions of KMF with recognized cellular receptors (Bose, Michael, Prashanth, & Chitraa, 2015). Synergistic amalgamations with other promising natural bioactive molecules could also be visually perceived as another prospective of future study to enhance the therapeutic potential of KMF (Tuli, Kashyap, & Sharma, 2015). Moreover, the role of KMF in modulating the expression and activity of drug metabolizing enzymes, such as CYPs could also avail the scientific communities to come forward to design novel strategies with subsisting chemotherapeutic agents (Bibi, 2008; Huang, Liangli, & Thomas, 2014; Zhang, Zheng, Zhu, Shen, & Zhu, 2006a, 2006b). Such approaches might be auxiliary in reducing the KMF-associated toxic (Canada, Watkins, & Nguyen, 1989; Silva et al., 1997) effects by lowering the requisite of active dosages. Furthermore, novel derivatives of KMF could additionally be an option to ameliorate the potency as well as dose-associated toxicity of this molecule. Rho and his colleagues have designed KMF predicated rhamnosides and purposed them as a paramount moiety in the obviation of inflammatory disorders (Rho et al., 2011). Lower potency of a drug has also been found to be associated with its

poor solubility and low bioavailability that can further be amended by utilizing the modern nanotechnology implements (Kuldeep & Ganju, 2014; Pinho, Martin, Graca, & Mariana, 2014). Luo et al. (2012a, 2012b) and Luo, Rankin, et al. (2012), have designed a novel nano-formulation for KMF utilizing Poly DL-lactic acid-co-glycolic acid, nanoparticles with amended bioavailability and cytotoxic effect against ovarian cancer (Luo et al., 2012a, 2012b; Luo, Rankin, et al., 2012). Moreover, the acerbic and astringent taste of most of the flavonoids could additionally be overcome by utilizing the nanotechnology mediated encapsulation processes which may further enhance their applicability on the more astronomically immense scale in aliment items (Munin and Edwards-Levy, 2011). Thus, KMF could prove to be a promising therapeutic agent and is certainly worth of further molecular studies.

Conflict of interest

None.

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