Pharmacological and Anticancer Potential of Black Ginger (*Kaempferia parviflora*) - Review Article

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Abstract

Kaempferia parviflora (KP), also known as Black ginger or Kra-chi-dum in Thailand, is a *Zingiberaceae* plant native to Thailand and Malaysia. This plant is commonly used by the community as a spice in cooking and healthy drinks for disease prevention and treatment. According to researches, KP extracts have broad bioactivities against infectious diseases caused by viruses and bacteria, as well as diseases related to metabolic disorders such as obesity, diabetes, aging, and gastrointestinal disorders. KP is also effective as an anticancer agent. This review article focuses on KP's anticancer activity and possible mechanisms of action. Furthermore, the botanical aspect and content of active compounds are investigated in this article. Considering KP's high potential as a medicinal plant, the potential interactions of KP with synthetic drugs and its potential formulation are investigated. According to the findings of this review, KP has anticancer and antimetastatic activity, and the active ingredient responsible for this activity is methoxyflavone.

Keywords: Anticancer, antiproliferative, black ginger, cytotoxic, *Kaempferia parviflora*.

Introduction

Cancer is a chronic disease with a rising incidence and mortality rate around the world. In general, cancer caused by genetic errors is closely related to a person's lifestyle[(1,2)]. At the moment, traditional cancer treatment remains a challenge[(3)]. These treatments are frequently associated with a variety of side effects, such as nausea, vomiting, dizziness, dry skin, and hair loss. Furthermore, the possibility of cancer recurrence causes patients who have survived to be fearful[(4)]. As a result, new treatments to treat prevent, and support cancer treatments are required. The use of medicinal plants is one promising method.

Kaempferia parviflora (KP), which is known as black ginger or Kra-chi-dum in Thailand, is a plant of the *Zingiberaceae* family that grows in Thailand and Malaysia[(5)]. This plant is commonly used by the community as a spice in cooking and healthy drinks for disease prevention and treatment. KP research indicates that extracts from KP have a wide range of activity in infectious diseases such as viral and bacterial infections, as well as metabolic diseases such as obesity, diabetes, ageing, and gastrointestinal disorders. KP is also an excellent energy booster and neuroprotectant. Furthermore, this plant has significant anticancer potential.

This article will go over KP's anticancer activity in detail, as well as its possible mechanisms of action. This article also covers the botanical aspect as well as the active compound content. Given that KP has the potential to be used as a medicinal plant; this article will discuss the possible interactions of KP when combined with synthetic drugs, as well as its possible formulation. Furthermore, this review will concentrate on studies that primarily investigate KP's potential anticancer activity and mechanism of action.

Research Methodology

This review article reports on KP plant activity based on studies published between 2005 and 2023. Using the keywords "*Kaempferia parviflora*," "Black ginger," "Kra-chai-dum," "anticancer," and "cytotoxic," literature was gathered from various online databases, including PubMed and Google Scholar. PubMed and Google

Scholar. To make it easier to find relevant references, the "PICO" technique was used, P (population/problem), I (intervention), C (comparison), and O (outcome)[6]. The study criteria are as follows: primary studies related to KP anticancer activity studies that are fully accessible. After sorting, about 51 research articles were summarized on KP activity and 14 research articles on KP anticancer activity in this review (Figure 1).

Kaempferia parviflora and its Botanical Aspect

Kaempferia parviflora is a rhizome plant belonging to the *Zingiberaceae* family. This plant comes from Burma, India, and Thailand. In Thailand, KP is referred to as Kra-Chai-Dum, black galingale, or thai ginseng. This plant is found in Loei Province and known as Thai Viagra or ginseng reference. KP is a 90 cm tall perennial ground herb with dark purple to black rhizomes, a brown exterior, and a distinct odour. Young plants have thin roots that grow into tubers, whereas storage roots are blotchy. Kra-chai-dahm refers to light purple to black KP (Figure 2). The sheath petiole is densely covered with red speckling on light green in the middle of the stems. Simple, densely alternate leaves with a dark-green upper epidermis, a light-green lower epidermis, and green petioles, the oldest of which are mottled with dark maroon. Flowers have a zygomorphic symmetry, are solitary, and have reddish purple or white pink bilabiate tuber, two bracts, six stamens, a long anther, a small style, and a stigma. They have a brass shape and are hairless, and when mature, the dehiscent fruit splits into three rays. The seeds are quite big [7].

The rhizome of KP is known as a health-promoting herb among locals in northeast Thailand as a traditional herbal plant. This plant is also used to treat colic, as well as peptic and duodenal ulcers. [8]. KP is commercially available as a tonic drink that can increase male sexual arousal. The use of KP to improve sexual ability, on the other hand, has been studied. Furthermore, KP (particularly the content of 5,7-dimethoxyflavone [DMF]) can inhibit phosphodiesterase-5 and phosphodiesterase-6, which are proteins involved in smooth muscle contraction and relaxation, and their effect is linked to sexual ability[9]. Additionally, it has been reported that a decoction of KP powder with alcohol can treat diarrhea, allergies, asthma, impotence, peptic ulcer, gout, dysentery, and diabetes[10]. Gout, aphthous ulcer, peptic ulcer, and abscesses are also treated with this rhizome [11].

Phytochemical constituent of *Kaempferia parviflora*

Methoxyflavones, a flavonoid isolated from the rhizome, are known to be the primary phytochemical of KP. This content is also a marker that is frequently used to identify KP. KP's biological activity is attributed to methoxyflavones such as dimethoxyfalvones (DMF), trimetoxyflavones (TMF), tertramethoxyflavones (TeMF), and pentamethoxyflavones (PMF). However, other compounds have been discovered through KP research.

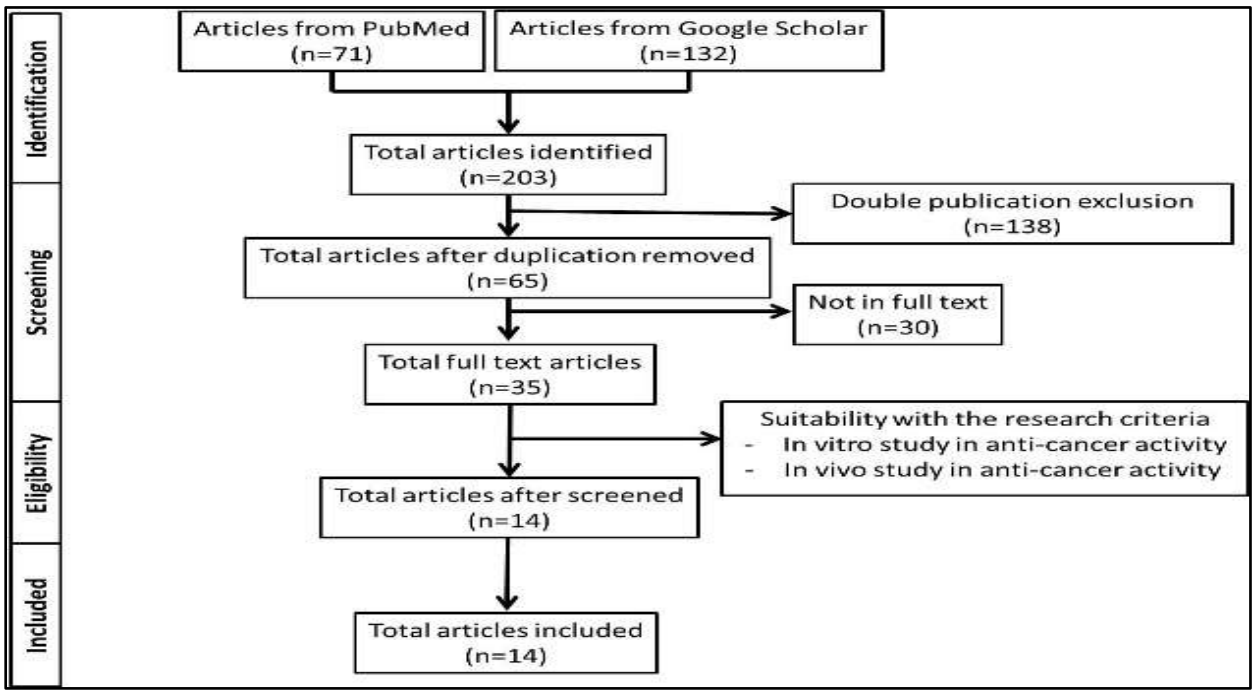


Figure 1. Flow diagram of selected articles

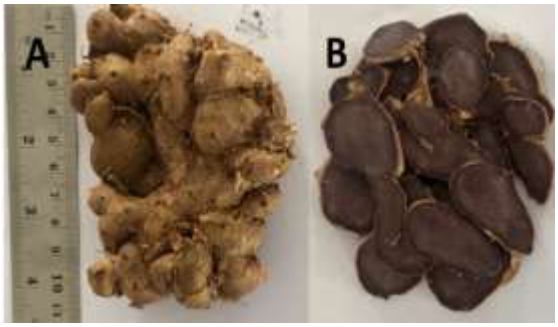


Figure 2. The whole rhizome (A) and cross section of *Kaempferia parviflora* (B)

Most studies focused on a single component of methoxyflavones isolated from KP. According to the study, compound 10 (5-hydroxy-3,7,3′,4′-tetramethoxyflavone) has antiallergic activity in the RBL-2H3 cell model via degranulation inhibition with an IC_{50} of 0.8 M [10]. In the study of compounds showed in figure 3 including compound 2, 3, 4, 5, 11, 13, and 15 related to their antiplasmodial, antifungal, antimycobacterial, and cytotoxic activities, compounds 3 and 4 showed antiplasmodial activities. Compound 4 also demonstrated antimycobacterial activity at a concentration of 50 mg/mL. Other compounds have been shown to be inactive. However, another study found that compound 5 had significant anti-fungal activity in dermatophyte fungi, with a MIC value of 250 mg/mL (Figure 3) [12].

Compounds 4 and 6 have also been shown to inhibit the activity of acetylcholinesterase and butyrylcholinesterase (Figure 3). These two compounds are dimethoxylated derivatives of 7-methoxyflavone at positions 3, 5, and 7 [13]. Aside from 7-methoxyflavone, compound 6 (5,7-DMF) was mostly altered and tested for activity. Some studies involving modifications to compound 6, such as amino, nitro, and oxime derivatization, show that this compound is responsible for KP's cytotoxic effect. The modified flavones and oxime derivate from compound 6 were found to have cytotoxic activity against KB and NCl-H187 human lung cancer cell lines, HEP-G2 hepatocellular carcinoma cell line, and T47D breast cancer cell lines[14,15]. Meanwhile, the amino and nitro modifications of Compound 6 exhibited cytotoxic activity on the KB human lung cancer cell line, with IC_{50} values of 6.80 and 5.84 μg/mL, respectively[16]. Furthermore, methylation at position 5 reduces methoxyflavone cytotoxicity in B16 melanoma 4A5 cells. As a result, Compound 11 has higher cytotoxicity than Compound 3[17].

Compound 4 has been identified as a cytotoxic agent. According to previous research, this compound has antiproliferative and antimetastatic properties against the human bile duct cancer cell lines HuCCA-1 and RMCCA-1. The researchers used a crude extract of KP in this study, but they stated that the crude extract contained 5,7,4′-trimethoxyflavone (TMF), which was responsible for the activity[18]. Another study found that compounds 2, 4, and 10 had cytotoxic activity on the HCT-15 human colorectal carcinoma cell line. This cytotoxic activity could be caused by caspase 3 activation in the intrinsic apoptosis pathway [19]. With a preferential cytotoxicity 50% (PC_{50}) value of 0.5-8.9 g/mL, compound 15 (5-hydroxy-7-methoxyflavone) demonstrated a unique activity that plays an important role in the "anti-austerity" of the PANC-1 human pancreatic cell line[20].

Promising Activity of *Kaempferia parviflora*

Several studies have been conducted to determine the biological activity of rhizome KP. These studies are at the *in vitro* and *in vivo* trial stages, and some have even progressed to clinical trials. KP rhizome has anti-acne, neuroprotective, anti-inflammatory, anti-allergy, blood fluidity, antiviral, and antibacterial activities, according to in vitro studies. In addition, an *in vivo* study found that the rhizome of KP has anti-gastric ulcer, anti-aging, anti-osteoarthritis, and neuroprotective properties. Several clinical studies have been reported on the activity of KP as an aphrodisiac, antidiabetic, and anti-obesity agent.

KP has traditionally been used in the form of a decoction and powder made from the roots. KP tonic drink, in particular, can improve sexuality and increase energy in men. *In vivo* studies on this activity have revealed an increase in running endurance in obese rat models [21,22]. Also reported clinical trials conducted on healthy elderly subjects, and the results showed that consumption of KP increased on the ability in chair stand test and walk. Another clinical study on adolescent student-athletes found that KP increased on the right-hand grip, maximal oxygen consumption and also back-leg strength.

Another clinical trial of KP was conducted to determine its anti-obesity and anti-diabetic activity. When compared to the placebo group, KP demonstrated anti-obesity activity in Japanese subjects by reducing abdominal fat [23]. This study is consistent with the previous *in vivo* test. *In vivo* studies on rats show the same result, namely a reduction in body weight gain and the abdominal fat accumulation and plasma triglycerides [24]. Meanwhile, on antidiabetic activity, clinical trials showed insignificant results in the administration of KP extract at 80–160 mg/kg BW with the placebo group [25-28]. This result is different from the results of the in vivo test conducted by M. Ochiai *et al* (2019), KP extract was found to increase plasma glucose and reduce fat accumulation in adipose tissue, liver, and muscles in an *in vivo* study using male diabetic NSY mice. The ability of polymethoxyflavones to bind to peroxisome proliferator-activated receptors (PPARs), which is

associated with insulin resistance and obesity, is thought to be responsible for their antiobesity and antidiabetic activity[27].

Aside from clinical research, several *in vitro* and *in vivo* studies have revealed that KP has a variety of activities. KP has been shown in animal studies to have neuroprotective, anti-osteoarthritic, anti-aging, and anti-gastric ulcer activity. Alzheimer's and dementia are diseases that cause people to lose their memories and cognitive abilities. These changes are caused by the progressive dysfunction and death of nerve cells, which are in charge of information storage and processing[29] . KP extract may help prevent this disease by increasing serotonin, norephinephrine, and dopamine levels. This trio of chemicals is critical for extending life and maintaining neuronal health[30]. KP phytochemicals, such as methoxyflavones, increased CRE (cAMP-response element) expression in nerve cell PC12D cells. In these cells, the CRE is involved in transcription[31].

KP extract demonstrated anti-osteoarthritis activity in a monoiodoacetic acid osteoarthritis model, similar to neuroprotective activity. KP extract has the ability to reduce pain threshold and osteoarthritis cartilage lesion[32].Furthermore, *in vitro* studies on chondrocyte cell lines revealed that the main component of KP (methoxyflavones) suppressed the expression of genes associated with inflammatory joint diseases such as NF-KB and MAPK[33].

In terms of anti-aging activity, KP extract inhibits cell-cycle inhibitors (p53, p21, p16, and pRb) while increasing the expression of cell-cycle activators (E2F1 and E2F2). This event allows cells to regenerate and prevents cell death(34). Changes in the structure of collagen, an important component of the extracellular matrix, are also linked to the occurrence of ageing. The structure of collagen changes with age, causing negative effects on biophysical and biomechanical properties due to the accumulation of advanced glycation end-products (AGEs). AGEs have been linked to non-enzymatic protein cross-linking, which alters the mechanical properties of the tissue[35]. KP extract can help to prevent the formation of wrinkles and the loss of collagen fibres. Increased collagen type I, III, and VII gene expression was used to achieve this activity. Furthermore, KP extract increased the expression of catalase, a skin antioxidant enzyme[36].

KP extract is known to have antibiotic activity *in vitro*, including anti-acne, antiviral, and antibacterial properties. Antibacterial activity is associated with anti-acne activity. Because the majority of acne cases are caused by a bacterial infection. Anti-acne activity was also demonstrated by KP by decreasing the expression of peroxisome proliferation-activating receptors (PPAR-γ) and oil-red O staining in sebocytes[37]. On antiviral activity, KP upregulation of TNF-a and IFN-b mRNA expressions, suggesting their roles in the inhibition of H5N1 virus replication[38]. Furthermore, KP demonstrated antibacterial activity by inhibiting the growth of *Cronobacter* spp. and EHEC. With increasing KP concentration, larger zones of inhibition of *Cronobacter* spp. and EHEC strains were observed[39].

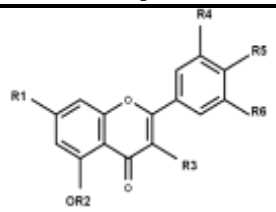
Anticancer Activity of *Kaempferia parviflora* and its Potential Mechanism of Action

Cancer treatment has a low success rate[3]. Chemotherapy for cancer treatment is widely used, but treatment using chemotherapy has many side effects; thus, using safer treatments is necessary[40]. At the moment, cancer treatment development is limited not only to the use of chemicals, but also to the ability of natural ingredients as the primary treatment, alternative medicine, complementary medicine, and leading compound sources to cancer prevention[41]. KP has been tested for anticancer activity in several types of cancer cells. KP also has antiproliferative, cytotoxic, and antimetastatic properties.

The antiproliferative activity of KP has been carried out in several cancer cell models such as HeLa (cervical cancer); SKOV3 (ovarian cancer); SNU-16, SNU-1, and AGS (human gastric cancer); HL-60 and U937 (human promyelocytic leukemia cancer); HuCCA-1 and RMCCA-1 (human bile duct cancer); PANC-1 (human pancreatic cancer); HCT-15 (human colorectal carcinoma); HEP-G2 (hepatocellular carcinoma); T47D, MCF-7 and 4T1 (breast cancer). KP showed potent and high antiproliferative activity in each of these cancers. In typical female cancers, KP shows IC_{50} values of 0.22 mg/mL (HeLa/cervical cancer), 0.53 mg/mL (SKOV3/ovarian cancer), and 22.94 µg/mL (T47D/breast cancer). The summary of anticancer activities of KP on various cancer cell lines is shown in Table 2.

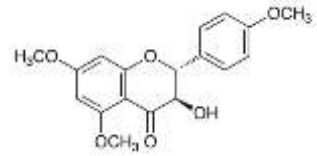
KP exerted antiproliferative and antimetastatic effects on HeLa cells. This antiproliferative effect was tested with a serial concentration of 0.01–1 mg/mL, and it began to show an inhibitory effect on cancer cell growth at a concentration of 0.08 mg/mL and a stable effect at a concentration of 0.5 mg/mL. Based on this test, IC_{50} was 0.22 mg/mL. This growth inhibition was confirmed by an increase in the number of apoptotic cells characterized by morphological changes from a normal round shape to oval, which began to not stick to the base of the disc. This finding was also supported by an increase in the number of apoptotic cells through flowcytometry at a concentration of 0.3 mg/mL by 39.8%±2.40% to 69.85%±3.04% at a concentration of 0.5 mg/mL. This apoptosis was associated with the induction of caspase 9 and 7 but not BID in the intrinsic pathway [42].

This research was continued, and at least ten bioactive compounds derived from methoxyflavones were discovered to be responsible for this activity. DMF, TMF, TMF, and PMF are among the methoxyflavone derivatives[43]. Another study found that a high polymethoxyflavone content in KP extracted with supercritical CO_2 had a stronger antiproliferative effect on HeLa cells than an ethanol extract. This antiproliferative activity outperformed quercetin as a positive control [44]. According to a recent study the ethanol extract of KP had a cytotoxic effect on MCF-7 and 4T1 cells by increasing apoptosis by binding to Bcl-2 and Bcl-XL proteins [45].

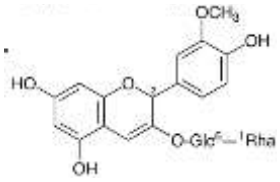


Structure of methoxyflavone

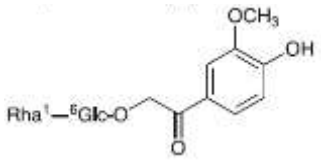
Name of compound	Subtitution					
	R1	R2	R3	R4	R5	R6
3,4,7,3',4'-pentamethoxyflavone (**1**)	$-OCH_3$	$-CH_3$	$-OCH_3$	$-OCH_3$	$-OCH_3$	-H
3,5,7,4'-tetrametoxyflavone (**2**)	$-OCH_3$	$-CH_3$	$-OCH_3$	-H	$-OCH_3$	-H
5,7,3',4'-tetramethoxyflavone (**3**)	$-OCH_3$	$-CH_3$	-H	$-OCH_3$	$-OCH_3$	-H
5,7,4'-trimethoxyflavone (**4**)	$-OCH_3$	$-CH_3$	-H	-H	$-OCH_3$	-H
3,5,7-trimethoxyflavone (**5**)	$-OCH_3$	$-CH_3$	$-OCH_3$	-H	-H	-H
5,7-dimethoxyflavone (**6**)	$-OCH_3$	$-CH_3$	-H	-H	-H	-H
3,5-dihydroxy-7,3',4'-trimethoxyflavone (**7**)	$-OCH_3$	-H	-OH	$-OCH_3$	$-OCH_3$	-H
5,3'-dihydroxy-3,7,4'-trimethoxyflavone (**8**)	$-OCH_3$	-H	$-OCH_3$	-OH	$-OCH_3$	-H
5,4'-dihydroxy-7-methoxyflavone (**9**)	$-OCH_3$	-H	-H	-H	-OH	-H
5-hydroxy-3,7,3',4'-tetramethoxyflavone (**10**)	$-OCH_3$	-H	$-OCH_3$	$-OCH_3$	$-OCH_3$	-H
5-hydroxy-7,3',4'-trimethoxyflavone (**11**)	$-OCH_3$	-H	-H	$-OCH_3$	$-OCH_3$	-H
5-hydroxy-3,7,4'-trimethoxyflavone (**12**)	$-OCH_3$	-H	$-OCH_3$	-H	$-OCH_3$	-H
5-hydroxy-3,7-dimethoxyflavone (**13**)	$-OCH_3$	-H	$-OCH_3$	-H	-H	-H
5-hydroxy-7,4'-dimethoxyflavone (**14**)	$-OCH_3$	-H	-H	-H	$-OCH_3$	-H
5-hydroxy-7-methoxyflavone (**15**)	$-OCH_3$	-H	-H	-H	-H	-H
4'-hydroxy-5,7-dimethoxyflavone (**16**)	$-OCH_3$	$-CH_3$	-H	-H	-OH	-H
Tilianine (**17**)	-OGlc	-H	-H	-H	$-OCH_3$	-H
Tamarixetin 3-O-rutinoside (**18**)	$-OCH_3$	-H	$-Rha^{1-6}Glc$	-OH	$-OCH_3$	-H
Syringetin 3-O-rutinoside (**19**)	$-OCH_3$	-H	$-Rha^{1-6}Glc$	$-OCH_3$	-OH	$-OCH_3$



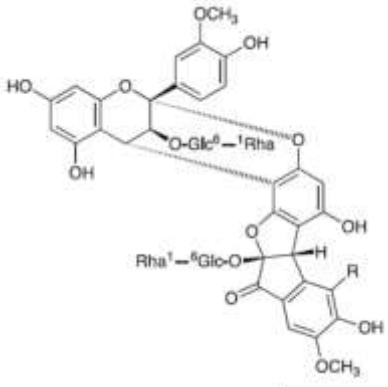
(*2R,3R*)-(-)-aromadendrin trimethyl ether (**20**)



Kaempferiaoside C (**26**) = 2R
Kaempferiaoside D (**27**) = 2S

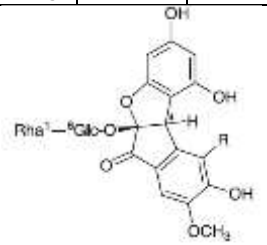


Kaempferiaoside E (**28**)

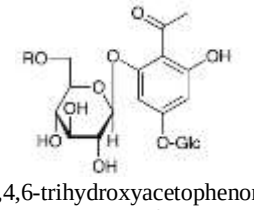


R=H (**21**)
Kaempferiaoside A (**22**) = R= OCH_3

Glc : β-D-glucopyranosyl
Rha : α-L-rhamnopyranosyl
Api : β-D-apiofuranosyl



4β-H, R=H (**23**)
4α-H, R=H (**24**)
Kaempferiaoside B (**25**) = 4β-H, R= OCH_3



2,4,6-trihydroxyacetophenone 2,4-di-O-β-D-gglucopyranoside (**29**) = R=H
Kaempferianoside F (**30**) = R=Api

Figure 3. Phytochemical constituents from the rhizome of *Kaempferia parviflora.*

Table 1. The summary on promising activities of *Kaempferia parviflora.*

No	Activity	Part of plant	Type of study	Biological activity	Reference
1.	Anti-acne (Anti-inflammatory and sebostatic)	Rhizome (ethanolic extract)	*In vitro* using murine macrophage-like (RAW264.7) and human keratinocyte (HaCaT) cell lines	The extract reduced the expression of inducible NO synthase (iNOS), pro-inflammatory cytokine tumour necrosis factor alpha (TNF- α), peroxisome proliferation-activating receptors (PPAR-γ) and cyclooxygenase-2 (COX-2). 5,7-dimethoxyflavone on KP, also influenced the expression of iNOS and NFKB signal molecules in human keratinocyte (HaCaT) cells stimulated by *P. acnes*.	(37)
2.	Antidiabetic	Rhizome (water, methanol, ethanol, aceton, hexane, ethylacetate extract)	*In vivo* using male diabetic Nagoya-Shibata-Yasuda mice (NSY mice) *In vitro* using nuclear receptor cofactor assay kit	On *in vivo* study, KP reduced fat accumulation in adipose tissues, liver, and muscles. Based on *in vitro* study, KP extract also showed PPAR-γ ligand-binding capacity, prevented insulin resistance and obesity.	(27)
		Dried powder of KP rhizome	Clinical trial on healthy subjects	There was no significant difference between giving KP 80 mg/kg BW, 160 mg/kg BW and placebo on glucose tolerance test. However, this study showed a pharmacokinetic profile to determine the safety of the use of KP.	(25)
3.	Aphrodisiac (Energy Enhancer)	Rhizome (ethanolic extract)	*In vitro* using L6Myotubes *In vivo* using C57BL/6J mice.	KP significantly increased mitochondrial density, peroxisome proliferator-activated receptor-c coactivator-1a (PGC1a), and induced the expression of mitochondrial biogenesis in L6 myotubes. KP extract improved running endurance and increased the skeletal muscle weight/body weight ratio.	(46)
		Dried powder of KP rhizome	Clinical trial on healthy elderly subjects	KP improved performance in the 30-second chair stand test and the 6-minute walk test. This result seems related to the reduced in oxidative stress by KP.	(22)
		Rhizome (ethanolic extract)	Clinical trial using adolescent student-athletes	KP extract increased right-hand grip strength, back-leg strength, and maximal oxygen consumption (VO2 max). Consumtion of KP also decreased time required for the 50-meter sprint test without affecting the sit-and-reach test or the 40-yard technical test.	(47)
4.	Neuroprotective	Rhizome (ethanolic extract)	*In vivo* using Sprague Dawley (SD) rats	When compared to the vehicle-treated group, KP increased serotonin, norepinephrine, and dopamine levels in the rat hippocampus.	(30)
		Rhizome (ethanolic extract)	*In vitro* using PC12D cells.	The constituent methoxyflavones of KP increased CRE (cAMP-response element (CRE))-mediated transcription in PC12D cells.	(31)
5.	Anti-osteoarthritis	Rhizome (ethanolic extract)	*In vivo* using mono-iodoacetic acid rat osteoarthritis model	KP reduced the pain threshold and severity of osteoarthritic cartilage lesions dan decreased the production of MMPs	(32)
		Rhizome (ethanolic extract)	*In vivo* using Freund's adjuvant-induced arthritis and a cartilage explant culture model Rats *In vitro* using human chondrocyte cell line	The KP extract reduced arthritis indexes in arthritis rats while having no effect on biological parameters. The KP extract demonstrated chondroprotective potential in the cartilage explant model by suppressing sulphated glycosaminoglycan release while maintaining high proteoglycan accumulation. A mixture of the major components of KP extract suppressed the expression of genes associated with inflammatory joint disease in human chondrocyte cell line.	(33)

6.	Anti-obesity	Rhizome (ethanolic extract)	*In vitro* using Wild-type C57BL/6J and ob/ob mice	KP reduced body weight, fat volume, and fat weight without affecting appetite. KP also inhibited the expression of adipogenic transcription factors and lipogenic enzymes by upregulating AMP-activated protein kinase (AMPK).	(48)
		Rhizome (ethanolic extract)	*In vivo* using rats	KP promotes energy metabolism at both doses by activating BAT and upregulating UCP1 protein at high doses. This effected on the reduction of body weigh, accumulation of intraabdominal fat and plasma triglyceride.	(24)
		Rhizome (ethanolic extract)	Clinical trial using Japanese subjects	After 12 weeks, the active KPE group had a significant reduction in abdominal fat area (visceral, subcutaneous, and total fat) and triglyceride levels when compared to the placebo group.	(23)
7.	Anti-inflamatory	Rhizome (ethanolic extract)	*In vitro* using R AW 264.7 cells	The ethanol extract of KP significantly inhibited PGE2 release, with an IC_{50} value of 9.2 g/mL. This plant extract and compound 5 also suppressed iNOS mRNA expression in a dose-dependent manner.	(11)
8.	Anti-aging	Rhizome (ethanolic extract)	*In vivo* using female hairless mice *In vitro* using Human dermal fibroblasts (Hs68)	KP increased cell growth while suppressing senescence-associated -galactosidase activation. Cell-cycle inhibitors (p53, p21, p16, and pRb) were inhibited, while cell-cycle activators (E2F1 and E2F2) were stimulated.	(34)
		Rhizome (ethanolic extract)	*In vivo* using female hairless mice	KP significantly prevented wrinkle formation and the loss of collagen fibers with increased type I, III, and VII collagen genes (COL1A1, COL3A1, and COL7A1). KP also increased the expression of antioxidant enzyme in skin, catalase; reduce the expression of inflammatory mediators, NF-κB, interleukin-1β (IL-1β), and COX-2.	(36)
9.	Anti-allergy	Component from KP rhizome (ethanolic extract)	*In vitro* using RBL-2H3 cells	With an IC_{50} value of 8.0 M, 5-Hydroxy-3,7,3′,4′-tetramethoxyflavone from KP had the highest anti-allergic activity against antigen-induced B-hexosaminidase.	(10)
10.	Anti-gastric ulcer	Rhizome (ethanolic extract)	*In vivo* using indomethacin, HCl/EtOH and water immersion restraint-stress in rats	Pretreatment with KP had no effect on gastric volume, pH, or acidity output in pylorus-ligated rats.	(49)
11.	Blood Fluidity Improvement	Rhizome (ethanolic extract)	*In vitro* using disseminated intravascular coagulation model	Using a disseminated intravascular coagulation model, KP reduced the blood passage time through a micro slit trough the activation of fibrinolysis.	(50)
12.	Antiviral	Rhizome (ethanolic and water extract)	*In vitro* using H5N1 virus	TNF-a and IFN-b mRNA expression were significantly increased by KP, implying that they play a role in inhibiting H5N1 virus replication.	(38)
13.	Antibacterial	Rhizome (ethanolic extract) and 7 compound from the KP extract	*In vitro* using human pathogens such as bacteria, yeast and dermatophyte fungi	The ethanolic extract of KP inhibited dermatophyte fungi but not the bacteria and yeasts tested. Furthermore, component 6 (3, 5, 7-trimethoxyflavone) in this extract demonstrated antifungal activity against three dermatophytes with MIC values of 250 mg/mL.	(12)
		Rhizome (ethanolic extract)	*In vitro* using *Cronobacter* spp. and enterohemorrhagic *Escherichia coli* (EHEC)	KP was found to have antibacterial activity against *Cronobacter* spp. and EHEC in dose dependent manner.	(39)

KP is also known to have antiproliferative and antimetastatic effects on a highly aggressive ovarian cancer cell SKOV3. At an IC_{50} of 0.55 mg/mL, KP inhibited the proliferation of SKOV3 ovarian cancer cells. Despite the presence of EGF during the experiment, this antiproliferative effect remained stable [51]. Similar to the effect of KP on HeLa cells, KP induces apoptosis in SKOV3 cells by inducing caspase-3, caspase-7, and caspase-9 (intrinsic pathway). Furthermore, because AKT and ERK1/2 phosphorylation was reduced, KP's antitumor activities may be regulated via the PI3K/AKT and MAPK pathways. KP also demonstrated antiproliferative activity via the intrinsic apoptotic pathway in human promonocytic leukaemia (U937), human urinary bladder cancer (T24), human promyelocytic leukaemia (HL-60), and human gastric cancer (SNU-16, SNU-1, and AGS)[50,51].

KP anticancer activity research employs not only crude extract, but also the major phytochemical content of KP. According to previous research, the main component of KP is methoxyflavones such as DMF, TMF, and TMF. These three types of methoxyflavones were purified and used as lead compounds, and their functional groups were modified to study their anticancer effects. Three types of methoxyflavone found in Karachidium Tea, namely 5,7-DMF, 5,7,40-TMF, and 3,5,7,30,40-PMF, demonstrated anticancer activity in human gastric cancer cells (SNU-16, SNU-1, and AGS), and TMF produces the best results [21]. In human lung cancer (KB), modified methoxyflavones (amino and nitro derivatives of 5,7-DMF and modified flavones [1c]) had an IC_{50} of 0.26 M at concentrations of 6.80 and 5.84 μg/mL. Another modified methoxyflavones was tested on hepatocellular carcinoma (HEP-G2) and breast cancer (T47D) and obtained IC_{50} of oxime derivatives 4 and 6, which were 36.38 and 25.34 μg/mL (HEP-G2) and 41.66 and 22.94 μg/mL (T47D)[15]. Compounds purified from the rhizome of KP, such as 3,5,7,4′-tetramethoxyflavone (TeMF), 5,7,4′-TMF, and 5-hydroxy-3,7,3′,4′ tetramethoxyflavone (5-H-TeMF), demonstrated antiproliferative activity against human colorectal carcinoma (HCT-15) by inducing cell apoptosis via the intrinsic These findings imply that methoxyflavones derived from KP could be used to develop an anticancer agent[19].

The unique activity of KP is its anti-austerity activity in the human pancreatic cancer cell line (PANC-1) [20]. Pancreatic tumor cells adapt to a nutrient-deficient microenvironment by changing their energy metabolism to tolerate severe nutrient deficiency. This is referred to as "austerity" in cancer biology [54]. KP showed anti-austerity activity through inhibition of cancer cell growth in nutrient-deprived medium with PC_{50} of 0.5–8.9 μg/mL. The results of the investigation also showed that KP could inhibit the formation of PANC-1 cell colonies. Tests were carried out to determine the content responsible for this activity, and 5-hydroxy-7-methoxyflavone was the best component with PC_{50} of 0.8 μM. This compound can be considered as a potential lead compound for the development of anticancer drug based on the anti-austerity strategy.

KP also showed antimetastatic activity. Several studies related to this activity have been conducted. KP showed antimetastatic activity in cervical cancer (HeLa), ovarian cancer (SKOV3), and human bile duct cancer (HuCCA-1 and RMCCA-1). These three cancers have a high proclivity to spread. In general, cancer cell metastasis is aided by the production of matrix metalloproteinases 2 and 9, which work by breaking down matrix proteins when cancer cells are about to metastasize[53,54]. In HeLa cells, KP showed an antimetastatic activity at a concentration of 0.1 mg/mL. This antimetastatic activity is due to KP-suppressed matrix metalloproteinase-2 production [42]. Similarly, in ovarian cancer cells (SKOV3), KP inhibited the activity of MMP-2 and MMP-9 at concentrations of 0.01–0.05 μg/mL [51]. On the contrary, in human bile duct cancer (HuCCA-1 and RMCCA-1), KP could block the movement of cancer cells when compared with controls, but this study did not include the possible mechanism of KP [18]. However, recent research suggested that KP's anti-migration activity was enabled by binding to the proteins ERK2 and FAK [45]. These two proteins are essential in the migration and metastasis of cancer cells [57]. Based on these studies, apart from being an anticancer, KP also has a great potential application as an anti-metastatic agent.

The main characteristic of cancer cells is the high ability of cancer cells to divide and proliferate[58]. Therefore, in cancer cells, the regulation and function of apoptosis are disturbed and even stopped [59]. Apoptosis is a hallmark of cancer, and it is a target in the development of anticancer agents. The induction of apoptosis can be divided into two, the extrinsic pathway or death receptor pathway and intrinsic or mitochondrial pathway [60]. KP shows cytotoxic activity in various cancer cells through the same mechanism, that is, the intrinsic pathway. Based on several studies that have been carried out, KP can induce apoptosis through inhibition on caspase 3, caspase 7, caspase 9, and also by binding with Bcl-2 and Bcl-XL. The induction of caspase 3, caspase 7, and caspase 9 will cause apoptosis of cancer cells (Figure 4). This process is also influenced by two other proteins: Bcl-2 and Bcl-XL. The presence of these two proteins in their free form can prevent apoptosis [61]. Thus, inhibition of Bcl-2 and Bcl-XL 'bonding' with a compound has immediate implications for the initiation of apoptotic events. This event may eventually prevent caspases 3, 7, and 9 from forming.

The intrinsic pathways that occur in cells can caused by internal stimuli such as irreversible genetic damage, hypoxia, high Ca^{2+} concentrations, and high oxidative stress[62]. These stimuli increase mitochondrial permeability and then release several pro-apoptotic molecules such as cytochrome-c, apoptosis-inducing factor, SMAC, DIABLO, and HtrA2 into the cytoplasm. Cytochrome-c molecule, APAF1, and pro-caspase-9 then form an apoptosome, which induces pro-caspase-9 change into caspase-9. The induction of caspase-9 causes the induction of caspase-3 and caspase-7, which in turn causes apoptosis. Based on literature review, KP primarily exerts a cytotoxic effect by influencing the intrinsic pathway for the induction of caspase-9, caspase-7, and caspase-3. This finding indicates that KP is most likely involved in the early stimulation of apoptotic intrinsic pathways such as DNA damage, ER stress, hypoxia, and metabolic stress (Figure 4).

Metastasis is defined as the movement of cancer cells from one organ to another in order to form new colonies[63]. In general, the occurrence of metastases is defined as the final stage of cancer progression[64]. Metastasis can begin with cell migration, cancer cell entry into blood vessels (intravasation), cancer cell entry into blood circulation (extravasation), and the formation of new colonies. This process is closely related to cancer cells' ability to digest and destroy extracellular matrix in order to facilitate cancer cell movement[65].

According to the literature review, KP has antimetastatic activity in various cancer cell models. This activity is thought to be associated with an increase in several proteins, particularly proteins involved in extracellular matrix breakdown, such as MMP-9 and MMP-2. Furthermore, according to *in silico* studies, there are components in KP that are thought to bind to two important proteins in the metastatic process, namely Extracellular signal-regulated kinases 2 (ERK) and Focal Adhesion Kinase (FAK). These two proteins are also involved in the production of MMP-9 and MMP-2.

MMP-9 and MMP-2 production can be activated in various ways, one of which is by activating Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) via the MEK1 and ERK1/2 pathways[66]. This pathway starts by phosphorylating the MEK1/ERK1/2 cascade, which then phosphorylates ERK1/2, activating NF-κB by removing IkB. Finally, the activated NF-κB/p65/p50 complex enters the nucleus, causing transcription and the production of Pro-MMP-9[67]. As a result, if a KP compound can bind to ERK 1/2, MMP-9 production and cell invasion can be reduced.

In addition to the MEK1 and ERK1/2 pathways, the FAK pathway can be used to activate NF-κB. FAK can activate the PI3K/AKT pathway, which in turn regulates NF-κB through mTOR. As a result, MMP-9 and MMP-2 expression may increase, making cancer cells more likely to metastasize[68] (Figure 4). FAK protein, in addition to being involved in MMP-9 and MMP-2 production, is also involved in cancer cell invasion and metastasis. It was stated that the FAK protein can trigger invasion and metastasis processes in several ways, namely functional interactions with Src family kinases, the recruitment of talin to nascent focal adhesions complexes, the formation of p130Cas/Cas/Crk complex and functional interactions with small G proteins, such as Ras homolog family member A (RhoA), Rac family small GTPase 1 (Rac1), and cell division cycle 42 (cdc42), to regulate actin cytoskeleton reorganisation[68].

Kaempferia parviflora interaction with synthetic drugs

The development of natural medicines aims to identify candidates for natural ingredients that can be used as prevention and treatment of diseases. However, in treating a disease, the initial stage of using natural ingredients is to determine whether the natural ingredients are toxic or have interactions with synthetic drugs that are commonly used. Furthermore, in pharmaceuticals, natural ingredients that have been proven effective must be formulated in order to be marketed. Given the enormous potential and activity of KP, it could be used as a complementary treatment with synthetic drugs and formulated in a dosage form that is acceptable to the patient.

The use of natural medicine could have milder side effects when compared with the use of synthetic drugs. Natural ingredients are also commonly consumed regularly to maintain and improve health. KP has many traditional uses, and it could improve health if consumed regularly. However, when using natural ingredients, their potential interactions with synthetic drugs or other treatments used by patients should also be considered. Table 3 shows several studies related to the interaction between KP and synthetic drugs commonly used by patients.

In a study conducted by Mekjaruskul and Sripanidkulchai (2015), KP could affect the absorption or the first fast effect of sildenafil on the intestine and liver or the combined effect of the two drugs. This result is due to a significant decrease in sildenafil levels by 95% in the initial administration with KP extract, and for subsequent administration, the levels of sildenafil are not affected and are the same as the control. This event may be due to the competition between KP and sildenafil for sildenafil transport via ATP-binding cassette transporters or organic anion transporting polypeptides at the start of administration, whereas subsequent administration of sildenafil could address this event. This phenomenon is also supported by the increase

in the level of active ingredients of KP (DMP, TMP, and PMP) in the blood at the beginning of administration. Meanwhile, after further administration, the levels of these three active ingredients seemed to decrease and stabilize[69]. KP has been reported to exert a large effect on the drug-metabolizing enzyme family cytochrome P450 (CYP) 3As and 2E1. This plant inhibits the performance of cytochrome P450 (CYP) 3As and 2E1; thus, the metabolism of drugs such as midazolam and acetaminophen is disrupted [70]. In a previous study, KP inhibits CYP2E1, which decreases blood levels of acetaminophen and increases the clearance of acetaminophen. Therefore, the effect of acetaminophen as a pain reliever is reduced because acetaminophen cannot reach an effective dose to provide its efficacy. KP-active ingredients, such as 5,7-dimethoxyflavone co-administration with midazolam, also significantly increased the blood concentration of midazolam about 130% compared with controls. The half-life time of midazolam is also 100 min longer compared with controls. Based on the research that has been conducted, conducting a study related to the interaction of KP with other drugs is necessary. Moreover, the concomitant use of KP as a food supplement and synthetic drug should show therapeutic and safety concerns because most synthetic drugs will experience a first fast effect in the liver by the CYP450 family of enzymes.

Apart from the CYP450 inhibitory effect given by KP, several researchers have also formulated KP, which can be marketed and well received by patients. In addition, this formulation was carried out to increase the absorption and efficacy of KP. The main component of KP, methoxyflavone, has a low intestinal absorption ability; thus, a formulation is necessary to increase its absorption. Most of the formulations carried out on KP and its active components aim to reduce the size of the components to micro and nano for use orally or transdermally.

The transdermal use of KP primarily aims to obtain its anti-inflammatory and pain-relieving activity. These activities are due to the content of methoxyflavone compounds present in KP. Methoxyflavones are poorly soluble in water, have low lipophilicity, and have low bioavailability [71,72]. The formulation of solid lipid nanoparticles (SLNs) was carried out by Sutthanut et al. (2009) on KP extracts using oils, surfactants, and PEGylating agents[71]. In addition, the flux values of three main flavonoids contained in the extract were greater when the KP extract was incorporated in SLNs. Another study conducted by Rangsimawong et al. (2018) used a microemulsion formulation, which was then reformulated into a micro-emulgel in the KP extract. In this study, methoxyflavone was also used as a marker. Based on the study conducted, microemulsions containing limonene 10% w/v showed methoxyflavone flux results, which were then continued to be formulated into micro-emulgels. The final result was obtained, that is, stable micro-emulgel extract[73].

Table 2. The summary on Anticancer activities of *Kaempferia parviflora* on various cancer cell lines.

NO	Effect	Mechanism	Cell line	Cancer type	Bioactive compound	Doses	Part of plant	Reference
1.	Antiproliferative	KP suppressed epidermal growth factor (EGF)-induced IL-6 secretion that caused the reduction level of Glycoprotein 130 (GP130), phosphorylated signal transducers and activators of transcription 3 (STAT3), and Mcl-1	HeLa	Cervical cancer	Methoxyflavones	IC_{50} 0.22 mg/mL	Rhizome (ethanolic extract)	(43)
2.	Antiproliferative	KP induced cell apoptosis through the intrinsic apoptosis pathway by activating caspase 9 and caspase 7	HeLa	Cervical cancer	NA	IC_{50} 0.22 mg/mL	Rhizome (ethanolic extract)	(42)
3.	Anti-metastasis	KP suppressed the matrix metalloproteinase-2 production	HeLa	Cervical cancer	NA	0.1 mg/mL	Rhizome (ethanolic extract)	(42)
4.	Antiproliferative	KP induced cell apoptosis through the intrinsic apoptosis pathway by activating caspase 9, caspase 3, and caspase 7	SKOV3	Ovarian cancer	NA	IC_{50} 0.53 ± 0.08 mg/mL	Rhizome (ethanolic extract)	(51)
5.	Anti-metastasis	KP inhibited the activity of MMP-2 and MMP-9	SKOV3	Ovarian cancer	NA	0.01 and 0.05 mg/mL	Rhizome (ethanolic extract)	(51)
6.	Antiproliferative	TMF induced cell apoptosis through the intrinsic apoptosis pathway by activating caspase 8, caspase 3 and caspase 7 and ER stress mediated apoptosis	SNU-16, SNU-1, AGS	Human gastric cancer	5,7-dimethoxyflavone (DMF), 5,7,40-trimethoxyflavone (TMF), and 3,5,7,30,40-pentamethoxyflavone (PMF). TMF give the best result.	-	Karachidium tea contain *K. parviflora* (water extract)	(21)
7.	Antiproliferative	KP induced cell apoptosis through the intrinsic apoptosis	HL-60	Human promyelocytic leukemic	NA	The IC_{50} for 24, 48 and 72 h were 25.5, 18.5 and 14.5 mg/mL	Rhizome (ethanolic extract)	(74)

		pathway by activating, caspase 3						
8.	Antiproliferative	KP induced cell apoptosis	HuCCA-1 and RMCCA-1)	Human bile duct cancer	5,7,4-Trimethoxyflavone (KP.8.10)	CC_{50} 46.1 g/mL (HuCCA-1) and 62.0 g/mL (RMCCA-1)	Rhizome (ethanolic extract)	(18)
9	Anti-metastasis	NA	HuCCA-1 and RMCCA-1)	Human bile duct cancer	5,7,4-Trimethoxyflavone (KP.8.10)	Crude extract (10–20 μg/mL) and KP.8.10 2.5–5 μg/mL)	Rhizome (ethanolic extract)	(75)
10.	Cytotoxic	NA	KB and NCI-H187	Human lung cancer	Modified flavones (1c)	IC_{50} on KB cell line was 0.26 μM and NCI-H187 0.014 μM	Modified flavones (1c) from the rhizome extract of *Kaempferia parviflora*	(15)
11.	Cytotoxic	NA	KB	Human lung cancer	Amino and Nitro Derivatives of 5,7-Dimethoxyflavone (*Ortho* aminophenols 6 and 8)	IC_{50} values of 6.80 and 5.84 μg/mL	Amino and Nitro Derivatives of 5,7-Dimethoxyflavone from the rhizome extract of *Kaempferia parviflora*	(16)
12.	Cytotoxic	KP extract induced cell death	T24	Human urinary bladder cancer	polyphenolic and flavonoid compounds	IC_{50} for ethanolic extract was 29.62 ± 1.13 μg/mL IC_{50} for water extract was 553.13 ± 20.53 μg/mL	Rhizome (ethanolic and water extract)	(53)
13	Antiproliferative	KP induced cell apoptosis through the intrinsic apoptosis pathway by activating, caspase 3	U937	Human promonocytic leukemic	NA	IC_{50} values at 24, 48 and 72 h of 92, 70 and 61 g/mL	Rhizome (ethanolic extract)	(74)
14.	anti-austerity	NA	PANC-1	Human pancreatic cancer cell line	5-hydroxy-7-methoxyflavone	PC_{50} values 0.5–8.9 μg/mL	Rhizome (ethanolic extract)	(20)
15.	Cytotoxic	TeMF, TMF, and 5-H-TeMF-induced cell apoptosis through the intrinsic apoptosis	HCT-15	Human colorectal carcinoma	3,5,7,4′-tetramethoxyflavone (TeMF), 5,7,4′-trimethoxyflavone (TMF),	NA	Purified compound from Rhizome (ethanolic extract)	(19))

		pathway by activating, caspase 3			and 5-hydroxy-3,7,3′,4′-tetramethoxyflavone (5-H-TeMF)			
16.	Cytotoxic	NA	HEP-G2 and T47D	Hepatocellular carcinoma and Breast cancer	Modified 5,7-Dimethoxyflavone	IC_{50} of oxime derivatives 4 and 6 on HEP-G2 cell was 36.38 and 25.34 µg/mL and T47D cell line 41.66 and 22.94 µg/mL	Modified 5,7-Dimethoxyflavone from Rhizome (ethanolic extract)	(14)
17.	Antiproliferative	NA	HeLa and AGS	Human cervical cancer and Gastric adenocarcinoma	5,7-Dimethoxyflavone	-	Rhizome (ethanolic and supercritical CO_2)	(44)
18.	Cytotoxic	HDMF, HTMF, Denbinobin, and Retusine-induced cell apoptosis through the intrinsic apoptosis pathway by binding to Bcl-2 and Bcl-XL	MCF-7 and 4T1	Human breast cancer	5-Hydroxy-7,4'-dimethoxyflavanone (HDMF), 5-Hydro-7,8,2'-trimethoxyflavanone (HTMF), Retusine and Denbinobin	IC_{50} of ethanol extract on MCF-7 cell was 138.43 µg/mL and 4T1 cell line 128.33 µg/mL	Rhizome (ethanolic extract)	(45)
19.	Anti-migration	HDMF, HTMF, Denbinobin, and Retusine inhibit the migration by binding to ERK2 and FAK	4T1	Human breast cancer	5-Hydroxy-7,4'-dimethoxyflavanone (HDMF), 5-Hydro-7,8,2'-trimethoxyflavanone (HTMF), Retusine and Denbinobin	Crude extract of KP inhibit the migration of 4T1 cell line on 32.5 and 62.5 µg/mL	Rhizome (ethanolic extract)	(45)

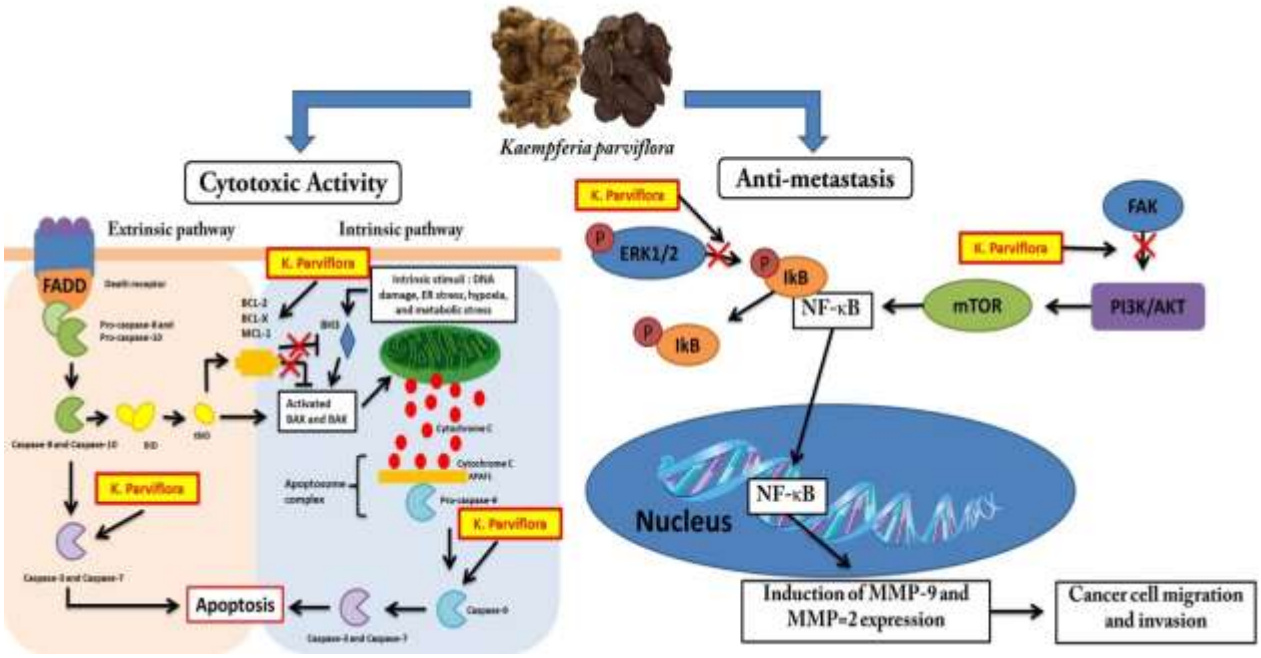


Figure 4. The possible anticancer mechanism of action from *Kaempferia parviflora*[45-62]

Table 3. The summary on *Kaempferia parviflora* interaction with synthetic drugs

No	Part of plant	Syntetic drug	Potential uses	Result	Reference
1	Rhizome (Ethanolic Extract)	Sildenafil	Erection dysfunction	Administration of KP extract reduced the sildenafil blood level at the first co-administration. KP extract also reduced AUC, C_{max}, and $t_{1/2}$ and increased the elimination rate constant. The concentration of PMF, TMF, and DMF also changed after co-administration of KP extract and sildenafil.	(69)
2.	5,7-dimethoxyflavone (DMF)	Midazolam	Anesthesia and sedatives	Administering DMF together with midazolam increased the blood concentration of midazolam about 130% compared with controls. The half-life time of midazolam is also 100 minutes longer compared with controls.	(76)
3.	Rhizome (Ethanolic Extract)	Acetaminophen	Analgesic and antipyretic	Administration of KP extract together with acetaminophen causes a decrease in blood levels of acetaminophen and increases the clearance of acetaminophen	(77)

Another transdermal formulation is the use of a isopropyl myristate-based (IPM) vehicle[78]. This formulation uses two types of vehicles, namely, ethanol/IPM and polyethylene glycol (PEG)/IPM. The results showed that vehicle ethanol/IPM had better solubility and permeation for methoxyflavones when compared with PEG/IPM with an optimal ratio of 1:9. Apart from using the IPM, Tuntiyasawasdikul et al. (2015) also carried out a unique formulation using a patch. In this study, a drug-in-adhesive patch was formulated for 13 types of KP load. The results showed that the formulated patch was stable, and it had satisfactory adhesive ability. If proven, then the best patch formulation is the use of 15% KP, 3% oleic acid, and 3% methanol[79].

In oral use, formulations that have been carried out to increase the bioavailability of KP are

using solid dispersion via solvent evaporation[80], self-nanoemulsifying (SNEDDS)[81], nano-suspension[82], self-microemulsifying (SMEDDS) , and complexation with 2-hydroxypropyl-β-cyclodextrin (CD)[72]. This oral formulation aims to obtain an appropriate formula that can increase the solubility and bioavailability of methoxyflavone. KP formulation in the form of SMEDDS and complexation with 2-hydroxypropyl-β-cyclodextrin provided good results, particularly with regard to methoxyflavone uptake into Caco-2 cells with Papp values 10- and 3.5-fold greater than KP without formulation, thereby increasing bioavailability with KP-SMEDDS formulations higher than those of KP (25.38-, 42.00-, and 26.01-fold for PMF, TMF, and DMF, respectively). For the KP-2-HP-CD complex, oral bioavailability was 21.63-, 34.20-, and 22.90-fold greater than that of KP. This result was similar to the KP-SNEDDS formulation. KP-SNEDDS formulation increased bioavailability 5.38-fold greater than KP alone. These results indicate the great application potential of the formulation of KP in increasing the bioavailability of its methoxyflavones.

Conclusion

KP has potential biological activities such as energy enhancer, sexual enhancer, anti-obesity, and anti-infection (caused by bacteria and viruses). In addition to these activities, KP exhibits excellent anticancer and antimetastatic properties. These activities may be due to the content of methoxyflavones. In anticancer activity, KP may affect the incidence of apoptosis by inducing caspase-3, caspase-7, and caspase-9. Meanwhile, its antimetastatic activity can reduce the expression of MMP-9 and MMP-2, thereby reducing the invasion and metastasis of cancer cells. Therefore, whether the material can be formulated must be investigated to ensure that a natural ingredient can be marketed. Methoxyflavones contained in KP have poor bioavailability, but formulations such as nanosuspension, SMEDDS, and complexation with 2-hydroxypropyl-β-cyclodextrin can be used to address this problem.

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Conflicts of Interest

The authors declare no conflict of interest.

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Author Contribution

The authors confirm contribution to the paper as follows: study conception and design: Indah H, Mohd F.A.B and Muhammad D; data collection: Indah H; analysis and interpretation of results: X. Indah H and Mohd F.A.B ; draft manuscript preparation: Indah H and Muhammad D. All authors reviewed the results and approved the final version of the manuscript.

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