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Insights on Anticancer Activities, Associated Phytochemicals and Potential Molecular Mechanisms of *Quisqualis indica*: A Mini Review

(Pandangan tentang Aktiviti Antikanser, Fitokimia Berkaitan dan Mekanisme Molekul Berpotensi *Quisqualis indica*: Suatu Kajian Mini)

YUAN SENG WU[1,2], MICHELLE FELICIA LEE[1,2], RHANYE MAC GUAD[3,*], FATHIMA ZAHRAA OZEER[1,2], APPALARAJU VELAGA[4], VETRISELVAN SUBRAMANIYAN[5,6], NEERAJ KUMAR FULORIA[7], SHIVKANYA FULORIA[7], KER WOON CHOY[8], SZE MENG LEE[4], SUBASH C.B. GOPINATH[9,10], AMITA VERMA[11] & TZE PHENG LAU[2]

[1]*Centre for Virus and Vaccine Research, School of Medical and Life Sciences, Sunway University, 47500 Petaling Jaya, Selangor, Malaysia*
[2]*Department of Biological Sciences, School of Medical and Life Sciences, Sunway University, 47500 Petaling Jaya, Selangor, Malaysia*
[3]*Department of Biomedical Science and Therapeutics, Faculty of Medicine and Health Science, Universiti Malaysia Sabah, 88400 Kota Kinabalu, Sabah, Malaysia*
[4]*Department of Medicinal Chemistry, Faculty of Pharmacy, MAHSA University, 42610 Jenjarom, Selangor, Malaysia*
[5]*Jeffrey Cheah School of Medicine and Health Sciences, Monash University Malaysia, Bandar Sunway, 47500 Subang Jaya, Selangor, Malaysia*
[6]*Center for Transdisciplinary Research, Department of Pharmacology, Saveetha Institute of Medical and Technical Sciences, Saveetha Dental College and Hospital, Saveetha University, Chennai, Tamil Nadu, 600077, India*
[7]*Faculty of Pharmacy, AIMST University, 08100 Bedong, Kedah, Malaysia*
[8]*Department of Anatomy, Faculty of Medicine, Universiti Teknologi MARA, 47000 Sungai Buloh, Selangor, Malaysia*
[9]*School of Bioprocess Engineering, Universiti Malaysia Perlis, 02600 Arau, Perlis, Malaysia*
[10]*Institute of Nano Electronic Engineering, Universiti Malaysia Perlis, 01000 Kangar, Perlis, Malaysia*
[11]*Department of Pharmaceutical Sciences, Sam Higginbottom University of Agriculture, Technology and Sciences, Prayagraj, India*

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ABSTRACT

Drug resistance is the main issue causing the treatment failure of anticancer drugs. This issue has urged researchers to search for new substances from medicinal plants, which are widely reported as the good sources of anticancer agents. *Quisqualis indica* is a plant belongs to Combretaceae family, known as Rangoon Creeper, which can be found abundantly in tropical countries and distributed profusely as a wild shrub. It has been widely used traditionally and scientifically claimed to process various therapeutic activities. It has recently been reported to possess various potential anticancer activities against different cancers. Looking at its availability in almost all seasons and grow fast, it is an arising source of herbal medicine in the discovery of anticancer drugs economically. Besides, *Q. indica* is enriched with several secondary metabolites of interest, which are responsible for the positive findings for its anticancer potentials. In this review, we aim to decipher and discuss the anticancer activities of *Q. indica* crude extracts and isolated phytochemicals as evidenced in preclinical models, as well as the associated molecular mechanisms. More preclinical investigations on its anticancer potentials should be conducted before translation to clinical testing.

Keywords: Anticancer; molecular mechanism; phytochemicals; phytotherapy; *Quisqualis indica*

ABSTRAK

Rintangan ubat adalah isu utama yang menyebabkan kegagalan rawatan ubat antikanser sintetik. Isu ini telah menggesa para penyelidik untuk mencari bahan baharu daripada tumbuhan ubatan yang dilaporkan secara meluas sebagai sumber agen antikanser yang baik. *Quisqualis indica* ialah tumbuhan daripada famili Combretaceae dan

dikenali sebagai Rangoon Creeper. Ia mudah ditemui di negara tropika dan bertaburan dengan banyak sebagai semak liar. *Q. indica* telah digunakan dengan meluas secara tradisi dan dibuktikan secara saintifik mempunyai pelbagai aktiviti terapeutik. Ia telah dilaporkan menunjukkan pelbagai aktiviti antikanser yang berpotensi terhadap pelbagai kanser. Melihat pada ketersediaannya dalam hampir semua musim dan berkembang pesat, ia merupakan sumber perubatan herba ekonomi dalam penemuan ubat-ubatan antikanser. Selain itu, *Q. indica* diperkaya dengan beberapa metabolit sekunder yang diminati dan bertanggungjawab terhadap penemuan positif potensi antikansernya. Ulasan ini bertujuan untuk menguraikan dan membincangkan aktiviti antikanser ekstrak mentah *Q. indica* dan fitokimia terpencil seperti yang dibuktikan dalam model praklinikal dan mekanisme molekul yang berkaitan. Penyelidikan masa depan boleh meliputi lebih banyak ujian praklinikal untuk lebih mengenai potensi antikansernya sebelum terjemahan kepada ujian klinikal.

Kata kunci: Antikanser; fitokimia; fitoterapi; mekanisme molekul; *Quisqualis indica*

Introduction

According to the World Health Organization (WHO), cancer is a leading cause of death globally, which contributed to approximately 10 million deaths in 2020 (World Health Organization 2022). Despite advances in various treatment options, chemotherapy remains as the preferred method. However, chemoresistance has contributed to 90% of chemotherapy failure during the metastasis and invasion stages (Housman et al. 2014; Wu et al. 2016). The development of newer synthetic chemotherapeutic agents is significantly stagnant and limited due to the complex mechanism of tumor cells, high cost, undesirable adverse events, low specificity, and toxicity, leading to less adherence to treatment if patient life quality is poor (Iqbal et al. 2017). With all things considered, an escalation of interest in using medicinal plants as an alternative approach has been reported as being safe, cost-effective, and causing lesser adverse effects (Ekor 2014).

Quisqualis indica Linn is a species from the Combretaceae family. *Quisqualis* stands for 'Which? What?' in Latin terms given by a Dutch botanist due to its odd behavior. The leaf size and flower color differentiate it; however, this species is exceptionally known to be a tropical vine, contributing to its common name called Rangoon Creeper. It is a shrub that is distributed widely all over the world, and thrives well in tropical locations, such as secondary forest areas and thickets throughout the Philippines (Sahu, Patel & Dubey 2012) and can be found in Malaysia, Myanmar, China, and Bangladesh. Traditionally, it has been widely used for tonsillitis, rheumatism, abdomen flatulence distention, helminthiasis, nephritis, cough, toothache gargle and birth control, ulcer boils and headache, urinary tract infection, diarrhea, and rickets (Bapuji & Ratnam 2009; Bose et al. 2009; Fiscal 2017; Gurib-Fakim 2012; Jadhav 2006; Lim 2015; Singh 2017; Van Sam, Baas & Keßler 2008). Besides, studies have reported that it contains many phytochemicals, such as alkaloids (e.g. trigonelline), flavonoids (e.g., rutin and pelargonidin-3-glucoside), terpenoids (e.g., ß-sitosterol and lupeol), amino acids (e.g., quisqualic acids and L-proline), tannins (e.g., quisqualin, ellagitannins and gallic acid), and fatty acids (e.g, oleic acids and linoleic acid), which may be responsible for the reported pharmacological activities (Bairagi et al. 2012; Lim 2015; Lin et al. 1997; Lohberger et al. 2015; Mahajan & Aher 2017; Rout, Naik & Rao 2008; Revathi & Radha 2018; Sahu, Patel & Dubey 2012).

This paper presents a detailed review of the anticancer activities of *Q. indica* as evidenced in preclinical models as well as the possible mechanisms of action, key molecules involved, and concentrations used. Furthermore, it discusses the phytochemicals of *Q. indica* that are directly or indirectly responsible for its anticancer potential against various cancers.

Quisqualis indica as a potential anticancer agent and its associated phytochemicals and molecular mechanisms

Under normal circumstances, one out of ten million cancer cells in a tumour mass have the possibility to inherit genetic resistance against a specific drug. Thus, it is expected that ten to one thousand cancer cells are resistant to anticancer drugs considering a clinically detectable tumour mass of one billion cells (Wang et al. 2019). In this section, the anticancer activity, concentrations tested, phytochemicals involved, and associated mechanisms of the crude extracts and phytochemicals of *Q. indica* in preclinical settings in several cancers, including breast, hepatocellular

carcinoma, prostate, skin, colorectal, soft tissue sarcoma, and leukemia are discussed and tabulated (Table 1). The chemical structures of associated phytochemicals are also depicted (Figure 1).

HEPATOCELLULAR CARCINOMA

Hepatocellular carcinoma (HCC) is known to be a primary cancer of the liver that contributes to the mortality cases reported in a population aged 63 to 65 (Jemal et al. 2011). The low treatment efficacy of chemotherapeutic agents, PIAF for instance, has led to the use of a combination strategy. However, such a regimen has reported causing several problems, such as intolerability of side effects and increased risk of chemoresistance (Yeo et al. 2005). Thus, the discovery of potential herbal products with less toxicity and economic is a good treatment alternative for HCC.

Several *in vitro* studies have demonstrated anticancer activities of *Q. indica* in HCC. For instance, Abd El-Rahman et al. (2016) unraveled the cytotoxic effects of *Q, indica* crude leaf extracts using different solvents and was assessed using brine shrimp lethality test (BSLT) and MTT assay against human HepG2 HCC cells. American Cancer Institute has reported that plant crude extracts with IC_{50} values less than 20 µg/mL are considered to be strongly cytotoxic. In the MTT assay, the IC_{50} values of dichloromethane (DCM) was 11.9 µg/mL and butanolic extracts (BuOH) was 17.9 µg/mL, showing that both extracts were strongly cytotoxic against HepG2 cells. Comparatively, moderate cytotoxicity was observed for defatted 90% methanol or MeOH (IC_{50} = 24.1 µg/mL), petroleum ether or PET (IC_{50} = 35.1 µg/mL), and ethyl acetate (EtOAc) (IC_{50} = 65.1 µg/mL). However, Park et al. (2002) showed that the cytotoxic effect of MeOH and aqueous (H_2O) extracts of whole *Q. indica* plant on both HCC HepG2 (IC_{50} = 350 µg/mL) and Hep3B (IC_{50} = 290 µg/mL) cells was weak (Park et al. 2002). This finding discrepancy could be explained by the possibility that non-polar molecules may be responsible for the anticancer activity of *Q. indica*. Studies have found that the organic solvents would have a significant impact on the total dry weight and extraction yield of plant parts (Zhang et al. 2020). Therefore, it is possible that different solvent extracts of *Q, indica* plant parts may contain different amounts of each phytochemical, thus giving different cytotoxicity effects.

Furthermore, two *in vitro* hepatoprotective studies further supported the cytoprotective potential of *Q. indica*. Song, Kim and Heo (2013) discovered that *Q. indica* fruit extract isolated using 70% MeOH positively protected HepG2 cells from ethanol-induced cytotoxicity and exhibited a cytoprotective effect of 1.3% toward ethanol-reduced cell viability (85.6%), indicating that *Q. indica* could protect the liver from developing diseases, such as cirrhosis and HCC. Similarly, Lee et al. (2017) showed that the ethanolic (EtOH) extract of *Q. indica* crude extract showed promising cytoprotection of 83.9% at 100 µg/mL for HepG2 cells. However, relatively less cytoprotective effect (20.6%) was observed when treated with a higher concentration (300 µg/mL). Heme-oxygenase-1 (HO-1) is a heme-degrading enzyme with anti-inflammatory, anti-apoptotic, and anti-proliferative functions. It was found that HO-1 induction is important to the cytoprotective mechanism against hepato-oxidative damage (Lee et al. 2017). The hepatoprotective mechanism was provided via the induction of nuclear factor E2 related factor 2 (Nrf2)-mediated HO-1 gene expression to scavenge high levels of reactive oxygen species (ROS) responsible for liver damage or cancer promotion (Gong, Cederbaum & Nieto 2004).

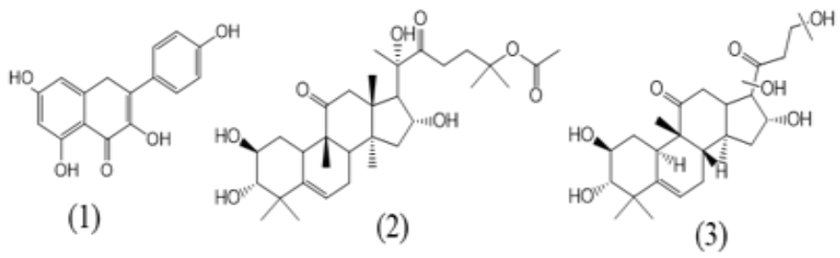

FIGURE 1. Phytochemicals involved in anticancer activities of *Q. indica*. (1) Kaempferol, (2) 25-O-acetyl-23,24-dihydro-cucurbitacin F, (3) 23, 24-dihydrocucurbitacin F

TABLE 1. Anticancer activity of *Q. indica* crude extracts or phytochemical with associated molecular mechanisms

Tested material	Solvent	Concentration	Test model	Isolated phytochemical	Mechanism	References
Leaf	MeOH, PET, defatted 90% MeOH, DCM, EtOAc, n-BuOH, H_2O	10-1000 µg/mL	*In vitro* (human HepG2 HCC cells)	Not available	Not available	Abd El-Rahman et al. (2016)
Whole plant	MeOH, H_2O	Not available	*In vitro* (human HepG2 and Hep3B HCC cells)	Not available	Not available	Park et al. (2002)
Fruit	70% MeOH	0.4% of the culture	*In vitro* (human HepG2 HCC cells treated with 1.3% EtOH)	Not available	Not available	Song, Kim & Heo (2013)
Whole plant	EtOH	100 µg/mL, 300 µg/mL	*In vitro* (human HepG2 HCC cells treated with tBHQ)	Not available	1. Reduced ROS levels via Nrf2-activated *HO-1* gene expression	Lee et al. (2017)
Leaf	EtOH (crude) followed by hx, EtOAc and H_2O	Not available	*In vitro* (human MCF-7 BC cells)	Tannins, saponins, terpenoids, flavonoids, cardiac glycosides, alkaloids	Not available	Luna, Limbo & Jacinto (2019)
Leaf and flower	EtOH (crude)	10 g/mL, 20 g/mL and 40 g/mL	*In vitro* (human MDA-MB-231)	Not available	Not available	Lanchhana, Ranjit & Kumar (2023)
Leaf	EtOH (crude) followed by hx, EtOAc and H_2O	Not available	*In vitro* (human HCT-116 CRC cells)	Tannins, saponins, terpenoids, flavonoids, cardiac glycosides, alkaloids	1. Induced apoptosis biomarker, DNA fragmentation	Luna, Limbo & Jacinto (2019)
Seed	70% EtOH	25-3200 µg/mL	*In vitro* (BPH in human LnCaP PC cells)	Not available	1. Decreased TP-induced AR and PSA levels	Ub Wijerathne et al. (2017)
		150 mg/kg	*In vivo* (TP-induced BHP in rats)		1. Reduced prostate weight, testosterone in serum, dihydrotestosterone concentration and *5α-reductase*; *type 2* gene expression in prostate tissue;	

					2. Attenuated TP-induced BPH; 3. Reduced protein levels of PCNA and cyclin D1; 4. Induced apoptosis by upregulating caspase 3 and 9, decreased, Bcl2/ Bax ratio; 5. Suppressed TP-induced p-AKT and glycogen synthase kinase 3β	
Flower	H_2O	40-120 µg/mL	*In vitro* using QCuNPs (human B16F melanoma cells)	Not available	1. Upregulated the expression of apoptotic genes (e.g., *caspase 3*, *caspase 9* and *Bax*) and proteins (e.g., CCDC8, CTLA4, ABRAXAS2, ANXA5, galectin-1, WDR11); 2. Upregulated the expression of cell cycle-related proteins (e.g., PCNA, 14-3-3γ, HSPA8)	Mukhopadhyay, Kazi & Debnath (2018)
Leaf, twig	Defatted PET	10 µg/mL	*In vitro* (human CCRF-CEM leukemia cells)	kaempferol, 25-O-acetyl-23,24-dihydro-cucurbitacin F and 23, 24-dihydrocucurbitacin F	Not available	Efferth et al. (2008)
Leaf, twig	Defatted PET	0-100 µg/mL	*In vitro* (human soft tissue sarcoma SW-872, SW-982, TE-671)	25-O-acetyl-23,24-dihydro-cucurbitacin F	1. Accumulated cells at G2/M cell cycle phase 2. Decreased cell cycle checkpoint regulators (e.g., cyclinB1, cyclinA, CDK1, CDK2) 3. Reduced apoptotic survivin gene and protein expression	Lohberger et al. (2015)

BREAST CANCER

According to the National Cancer Institute, or NCI (2019), breast cancer (BC) is one of the most common cancers diagnosed in women, accounting for more than one in ten new diagnosed cases every year. Typically, the most aggressive type of cancer, triple negative breast cancer (TNBC) is resistant to the standard chemotherapeutic agents targeting these receptors (Wahba & El-Hadaad 2015).

The anticancer activity of *Q. indica* leaf crude extracts against human MCF-7 breast cancer cells was reported by Luna, Limbo and Jacinto (2019). The crude extracts were prepared using different organic solvents, such as hexane (hx), EtOAc, and water. All treatments with IC_{50} values of less than 30 µg/mL were considered active. The crude extract which consisted of phytochemicals such as alkaloids, cardiac glycosides, flavonoids, tannins, and terpenoids did not exhibit any significant cytotoxicity against MCF-7 cells. Therefore, the hx extract containing phytochemicals such as alkaloids, cardiac glycosides, flavonoids, and terpenoids, was further fractionated using isocratic column chromatography to generate eight fractions. The results showed that only isocratic fraction (IF) 4 of hx extract (IC_{50} = 13.33 µg/mL) was significantly cytotoxic against MCF-7 cells, while IF 8 had an IC_{50} value between 30 and 40 µg/mL. Furthermore, IF 4 was further subjected to gradient silica gel column chromatography to generate six fractions (GF 6a to 6f). Among six sub-fractions, GF 6e (IC_{50} = 4.69 µg/mL) and GF 6f (IC_{50} = 4.78 µg/mL) exhibited potent cytotoxicity against MCF-7 cells. Furthermore, the phytochemical testing indicated the presence of alkaloids, flavonoids, and cardiac glycoside, which may be responsible for the observed significant cytotoxic effect against MCF-7 cells (Luna, Limbo & Jacinto 2019). The emergence of cytotoxicity of the isocratic fractions and sub-fractions even though the crude extract did not exhibit any significant cytotoxicity against MCF-7 cells could be due to antagonistic interactions between these fractions. When the MCF-7 cells were subjected to treatment with these fractions separately, cytotoxicity was then observed (Sang et al. 2006).

In another study by Lanchhana, Ranjit and Kumar (2023), the anticancer activity of *Q. indica* leaf and flower crude extracts were investigated against another human breast cancer cell line, MDA-MB-231. The *Q. indica* crude extracts were prepared using ethanol and the final tested concentrations were 10 g/mL, 20 g/mL, 40 g/mL, and 80 g/mL. No cytotoxicity was observed against the MDA-MB-231 cells for concentrations of 10 g/mL, 20 g/mL, and 40 g/mL of the *Q. indica* crude extracts. Approximately 20% cytotoxicity was observed against the MDA-MB-231 cells for concentration of 80 g/mL of the *Q. indica* crude extracts. The IC_{50} value for treatment of MDA-MB-231 cells with the *Q. indica* crude extracts was estimated to be >100 µg/ml. However, further studies are warranted to identify the phytochemicals responsible for the anticancer activity and their specific mechanisms of action (Lanchhana, Ranjit & Kumar 2023).

COLORECTAL CANCER

Colorectal cancer (CRC) is the fourth most commonly occurring cancer among males and females worldwide (Van der Jeught et al. 2018). The primary chemotherapeutic agent for CRC is 5-FU (Salonga et al. 2000), while its combination with oxaliplatin and irinotecan was given to advanced-stage patients (Yaffee et al. 2015). Although there is an improvement to existing therapy, the 5-year survival rate is only 12% as nearly half of the advanced stage CRC patients are 5-FU resistant (Douillard et al. 2000; Siegel, Miller & Jemal 2016).

Luna, Limbo and Jacinto (2019) further showed the potent anticancer potential of *Q. indica* leaf extracts in human HCT-116 CRC cells. The results showed that strong cytotoxicity was exhibited by ethanolic (EtOH) extract (IC_{50} = 11.48 µg/mL) and hx extract (IC_{50} = 7.81 µg/mL). Only five fractions (i.e., IF 1, IF 2, IF 4, IF 5, and IF 6) exhibited potent cytotoxicity, with IF 4 (IC_{50} = 10.90 µg/mL) and IF 5 (IC_{50} = 9.43 µg/mL) showing the highest cytotoxic effect. Similar to the results obtained from BC, IF 4 was further sub-fractioned. Interestingly, GF 6d (IC_{50} = 20.38 µg/mL) was selected for TUNEL assay to detect DNA fragmentation, which is an apoptosis biomarker, although GF 6e (IC_{50} = 5.07 µg/mL) and GF 6f (IC_{50} = 8.77 µg/mL) showed better cytotoxicity. Similarly, phytochemical screening suggested the cytotoxic effect of *Q. indica* leaf extracts could be contributed by flavonoids, alkaloids, and cardiac glycosides.

PROSTATE CANCER

Prostate cancer (PC) is ranked the third most common type of cancer among males, with an estimation of 1,414,259 new cases estimated for the year 2020 (IARC 2022) and was further reported to have caused 375,304 deaths in 2020 (Wang et al. 2022). Taxane is the mainstay

chemotherapeutic agent for PC, but its treatment outcome is impeded by various chemoresistance mechanisms (Fitzpatrick & De Wit 2014). Currently, docetaxel is the only approved FDA chemotherapeutic agent, but it can only maintain a survival rate of 7 months on average, with several clinical side effects (Kahn, Collazo & Kyprianou 2014; Malik et al. 2015).

The anticancer activity of *Q. indica* in PC has been unveiled by Ub Wijerathne et al. (2017) using *in vitro* and *in vivo* models. They extracted *Q. indica* seeds with 70% EtOH before testing its cytotoxic effect using different concentrations on benign prostatic hyperplasia (BPH) in human LnCaP PC cells (25 to 3200 µg/mL) and testosterone propionate (TP)-induced BPH rat model (150 mg/kg). In MTT assay, *Q. indica* treatment did not significantly decrease in LnCaP cell viability, with only 3200 µg/mL causing 37.2% reduction. The high expression of androgen receptor (AR) and prostate specific antigen (PSA) induced by testosterone was remarkably suppressed after treating with 50 µg/mL of *Q. indica* seed extract. The TP-induced rat models exhibited high expression of proliferating cell nuclear antigen (PCNA) and cyclin D1 proteins in BHP tissue, which was similarly observed in PC tissue. In fact, PCNA is known to regulate cell proliferation and implicated in PC clinical grade (Wang et al. 2011). Intriguingly after *Q. indica* treatment, downregulated PCNA and cyclin D1 and upregulated pro-apoptotic protein, such as B-cell lymphoma 2 (Bcl-2), Bcl-2-associated X protein (Bax), caspase-3 and caspase-9, were observed.

SKIN CANCER

The most aggressive type of skin cancer is melanoma and is the 17th most common cancer worldwide, as it is resistant to both chemotherapy and radiotherapy with 150,000 new melanoma cases in 2020 (Kalal, Upadhya & Pai 2017; World Cancer Research Fund International 2022). The main mechanism for melanoma chemoresistance is due to deregulated apoptosis induction (Grossman & Altieri 2001). The anticancer activity against human B16F10 melanoma cells by copper nanoparticles (QCuNPs) synthesized using the H_2O flower extract of *Q. indica* has been recently reported by Mukhopadhyay, Kazi and Debnath (2018). The B16F10 cell viability was decreased in a dose-dependent manner from 40 to 120 µg/mL, with the IC_{50} of 102 µg/mL. Interestingly, QCuNPs was non-toxic to normal mouse embryonic fibroblast (NiH3T3) as a minimal reduction in cell viability was observed at 120 µg/mL. This finding is verified in LDH assay in which QCuNPs dose-dependently (0 to 120 µg/mL) induced LDH leakage in B16F10 cells. It was interesting to note that nearly 50% of QCuNPs-treated B16F10 cells were apoptotic or in cell cycle arrest as evidenced with the upregulation of apoptotic genes (i.e., *caspase 3*, *caspase 9*, and *Bax*) and proteins (i.e., coiled-coil domain containing-8 (CCDC8), CTLA4, BRISC complex subunit Abro1 (ABRAXAS2), anxa5 protein (ANXA5), galectin-1, and WD repeat-containing protein 11 (WDR11), together with the downregulation of cell cycle arrest-related proteins (i.e., PCNA, 14-3-3 protein gamma (14-3-3γ), prohibitin, and heat shock cognate 71 kDa protein (HSPA8)). The induction of cytotoxicity and apoptosis was mediated by oxidative stress as evidenced with high ROS levels and low glutathione levels. However, QCuNPs did not significantly inhibit tumor growth in mice bearing B16F10 cells (Mukhopadhyay, Kazi & Debnath 2018).

LEUKEMIA

NCI statistics have reported that leukemia is the tenth most commonly occurring cancer worldwide and has contributed to 3.4% of all new cases in the US (Caiado et al. 2019). Chemoresistance of leukemia arises from genetic variation, making many clinicians and researchers screening into the impact of mutation (Almeida & Ramos 2016). However, this approach is not extensively studied and complex, leading to the elderly getting the appropriate treatment late that consequently increases the mortality risk.

Efferth et al. (2008) investigated the anticancer potential of *Q. indica* twig and leaf crude extracts isolated by defatted PET followed by EtOAc against human CCRF-CEM leukemia cells. The combined leaf and twig crude extracts were tested at 10 µg/mL, and the cell proliferation was reduced by approximately 20%. It interestingly showed that out of seven phytochemicals isolated from the crude extracts of *Q. indica*, kaempferol, 25-O-acetyl-23,24-dihydro-cucurbitacin F and 23, 24-dihydrocucurbitacin F, inhibited cell proliferation significantly, with 25-O-acetyl-23,24-dihydro-cucurbitacin F identified to exhibit the strongest cytotoxicity. Nonetheless, the researcher did not further investigate the possible molecular mechanisms underlying anti-leukemia of these phytochemicals.

SOFT TISSUE SARCOMA

Soft tissue sarcoma (STS) is a rare malignancy representing only 0.7% of all new cancer cases in the

US, as reported in NCI statistics. Because metastasis is also widespread in STS, chemotherapy is the treatment option for palliative care (Reed & Altiok 2011). The combination of doxorubicin and ifosfamide is the first-line treatment for advanced metastatic cases but limited by adverse toxicity, and some STS subtypes are anthracycline resistant. Thus, alternative medicine, such as specific-histology-based drugs (pazopanib) is given, but it is costly and still under clinical trials (In, Hu & Tseng 2017).

One study has reported the anticancer activity of *Q. indica* in STS using *in vitro* models (Lohberger et al. 2015). In the study, 25-O-acetyl-23,24-dihydro-cucurbitacin F from *Q. indica* leaves and twigs was isolated before examining its cytotoxicity on three human STS cells, including SW-872 liposarcoma cells, SW-982 synovial sarcoma cells, and TE-671 rhabdomyosarcoma cells. After treating with this phytochemical (0 to 100 µg/mL), the cell viability was reduced in a dose-dependent manner, with the IC_{50} values of 9.1 µg/mL (SW-872), 2.4 µg/mL (SW-982), and 0.7 µg/mL (TE-671), respectively. Besides, a high number of cells was arrested at G2/M phase which led to reduced gene and protein levels of cell cycle-related checkpoint regulators, such as cyclin-dependent kinase 1 (CDK1), CDK2, cyclin A, and cyclin B1. The gene and protein expression of Survivin, which plays a crucial role in mitosis and cell survival regulation, were also downregulated significantly by this phytochemical. The result further showed that 25-O-acetyl-23,24-dihydro-cucurbitacin F promoted the expression of apoptotic caspase-3 dose-dependently in SW-872 and TE-671 cells.

Conclusion

In this paper, the anticancer potential of *Q. indica*, possible associated molecular mechanisms, and phytochemicals involved were discussed. The anticancer activity of *Q. indica* has been evaluated mostly using *in vitro* models against liver, breast, colorectal, prostate, skin, leukemia cancers, and soft tissue sarcoma, with relatively more studies in HCC. Collectively, this review paper has provided a clear insight that *Q. indica* is a potential anticancer and is suggested for all parts of *Q. indica* to be examined using different polarity solvents to obtain a complete therapeutic profile. Future research may need to test the anticancer potentials of *Q. indica* against more cancers using different preclinical models as well as pharmacokinetic profile and toxicity. Besides, the molecular mechanisms underlying its anticancer activity should also be determined further before clinical testing. The issues of bioavailability, drug design, and nano-formulation in order to achieve successful clinical outcomes should also be tested and addressed.

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*Corresponding author; email: rhanye@ums.edu.my