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Review Article

COROSOLIC ACID: A SYNOPSIS ON ITS ANTICANCER PROPERTIES

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ABSTRACT

Corosolic acid (CA) or 2β-hydroxyursolic acid is an ursane-type pentacyclic triterpene with a molecular formula of $C_{30}H_{48}O_4$ and molecular weight of 473 g/mol. The 30-carbon skeleton and five six-membered rings (A–E) of CA are structurally similar to those of ursolic acid, asiatic acid, and 23-hydroxyl CA. CA was first isolated from the leaf of *Lagerstroemia speciosa* and later from the fruit of *Crataegus pinnatifida*. Although *L. speciosa* (Lythraceae) remains the most important source of CA, Rosaceae and Lamiaceae are the dominant families. This synopsis is focused on the anticancer properties of CA as recent studies have generated new and additional knowledge on its oncology. CA has antitumor, antiproliferative, and apoptotic activities against many types of human cancer cells (including some murine cancer cells), which are inhibited through different molecular mechanisms. Non-apoptotic cell death has also been reported. Depending on the type of cancer cells, the cytotoxicity of CA is comparable to ursolic acid, its analog. Currently, there are no studies on the structure-activity relationship of CA. In ursolic acid, which is structurally similar to CA, the –OH group at C-3 and the –COOH group at C-28 exhibited cytotoxic activity.

Keywords: Corosolic acid, Pentacyclic triterpene, Apoptosis, Non-apoptotic cell death.

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INTRODUCTION

Terpenes are one of the most widespread groups of natural products. Triterpenes, a group of terpenes, often have pentacyclic or tetracyclic structures. Pentacyclic triterpenes can be classified into lupane, oleanane, and ursane types. These compounds possess pharmacological properties, including anti-inflammatory, antioxidant, antiviral, antidiabetic, antitumor, anti-ulcerogenic, analgesic, hepatoprotective, and cardioprotective activities. There are several recent reviews on pentacyclic triterpenes, providing useful information on their natural occurrence, chemistry, and beneficial health effects [1-3]. Information in these reviews includes the ursane type of pentacyclic triterpenes, of which corosolic acid (CA) belongs.

Pharmacological activities of CA include antidiabetic [4,5], antibacterial [6], anti-inflammatory [7-9], anti-obesity [9-11], anti-atherosclerosis [7,12], cholesterol-reducing [13], osteoblast differentiation [14], antioxidant [15,16], and hepatoprotective [16,17] properties. Among these biological activities, the antidiabetic properties of CA are well documented [18-25] with several clinical trials conducted [26,27] and patents applied [28-32]. The beneficial effects of CA toward glucose and lipid metabolism involve multiple mechanisms such as enhanced cellular uptake of glucose, impaired hydrolysis of sucrose and starch, decreased gluconeogenesis, and regulation of lipid metabolism [4,5].

This synopsis is focused on the anticancer properties of CA as recent studies have generated new and additional knowledge on its oncology. This short review gives up-to-date data and information for scientists to conduct further research on CA and other pentacyclic triterpenes with similar molecular structures. The anticancer properties of CA have not yet been reviewed. There are several reviews on the anticancer properties of triterpenes. They include a review on ursane-type pentacyclic triterpenoids as useful platforms to discover anticancer drugs [33] and another review on triterpenes as potentially cytotoxic compounds [34].

COROSOLIC ACID

CA is an ursane-type pentacyclic triterpene with a molecular formula of $C_{30}H_{48}O_4$ and molecular weight of 473 g/mol [35]. The 30-carbon skeleton comprises five six-membered rings (A–E). Structurally, CA is similar to ursolic acid, asiatic acid, and 23-hydroxyl CA (Fig. 1). Differences between these four pentacyclic triterpenes are in R_1 and R_2 of C-2 and C-23, respectively.

CA was first isolated from the leaf of *Lagerstroemia speciosa* [36] and later from the fruit of *Crataegus pinnatifida* [37]. A literature search for plant species containing CA was conducted and several interesting trends emerged. Leaves of *L. speciosa* remain the most important source of CA [19,38,39]. Surprisingly, no other species of the family Lythraceae, which *L. speciosa* belongs, have been reported. Among the 40 species reported in the literature, Rosaceae (16 species) and Lamiaceae (six species) are the dominant families. Species of Rosaceae belong to the genera of *Agrimonia*, *Chaenomeles*, *Crataegus*, *Eriobotrya*, *Potentilla*, *Prunus*, *Pyrus,* and *Rubus*. Species of Lamiaceae are of the genera *Glechoma*, *Hyssopus*, *Orthosiphon*, *Perilla*, *Phlomis,* and *Salvia*. This indicates that species of Rosaceae and Lamiaceae are rich in CA.

Native to South and Southeast Asia, *L. speciosa* is a semi-deciduous small- to medium-sized tree with obovate leaves that are opposite [40,41]. During each rainy season, trees would produce flushes of new leaves that are brilliant red in color (Fig. 2) before turning green. Borne on large, axillary, or terminal panicles, the attractive flowers have wrinkled pink or purple petals and yellow stamens (Fig. 3). Flowers emit a faint honey-like fragrance. Locally known as arjuna in India, bungur in Malaysia, Singapore, and Indonesia, ta-bak in Thailand, and banaba in the Philippines, *L. speciosa* is a common ornamental tree planted along roadsides, and in gardens and parks. The species has been traditionally used in folk medicine as a remedy for illnesses and ailments, particularly for lowering blood sugar level and reducing body weight, and as a remedy for diabetes [40].

In Thailand, the content of CA in *L. speciosa* leaves ranged from 0.01% to 0.75%, depending on the location and season of sampling [42]. In the Philippines, CA content of young red leaves of *L. speciosa* (58 μg/g) was almost 1.9 times that of mature green leaves (31 μg/g) and 1.5 times that of flowers (38 μg/g) [43]. The redness of young leaves was due to cyanidin 3-*O*-glucoside, the anthocyanin identified in the species for the

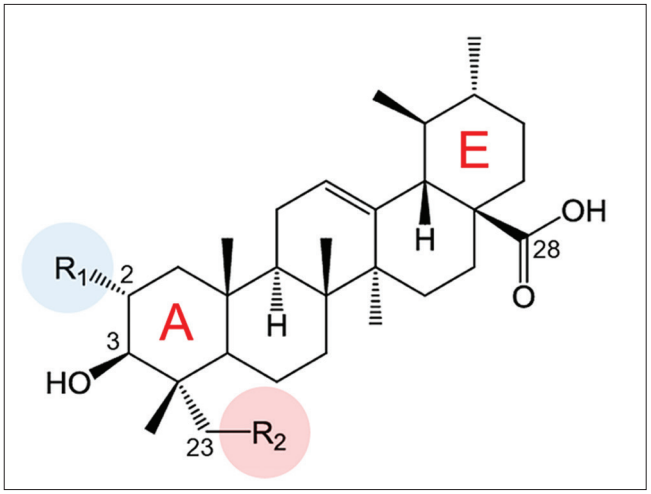

Fig. 1: Corosolic acid and other pentacyclic triterpenes with similar molecular structures

Fig. 2: *Lagerstroemia speciosa* (banaba) tree with brilliant red young leaf flushes

Fig. 3: (a and b) *Lagerstroemia speciosa* with attractive pink (left) and purple (right) flowers

first time. There was a strong correlation (R=0.877) between the contents of CA and cyanidin 3-*O*-glucoside. Rich in CA, red leaves of *L. speciosa* are used for producing high-quality red banaba tea in the Philippines. Of 38 different plant extracts that are commercially available as dietary supplements, the content of CA was the highest in leaves of *L. speciosa* (14233 mg/kg), followed by aerial parts of *Orthosiphon stamineus* (1132 mg/kg) and flowers of *Crataegus monogyna* (993 mg/kg) [44]. In capsules and tablets containing *L. speciosa*, the content of CA ranged from 0.02 to 0.18 mg per capsule or tablet [45]. In leaves of *Eriobotrya japonica*, the content of CA was reported to be 0.36% [46].

ANTICANCER PROPERTIES

Cancer has six hallmark features of sustaining proliferative signaling, evading growth suppressors, resisting cell death, enabling replicative immortality, inducing angiogenesis, and activating invasion and metastasis [47,48]. Phytochemicals such as flavonoids [49], triterpenes including CA [50], and sesquiterpenes including zerumbone [51] that show promise as anticancer agents should be able to overcome one or several of these hallmark features.

CA isolated from the fruit of *C. pinnatifida* displayed cytotoxicity against HepG2 liver, SNU-C4 colorectal, HeLa S3 cervical, and K-562 leukemia cancer cells with ED_{50} values of 4.8, 0.4, 1.0, and 4.3 µg/ml, respectively [37]. From the stem bark of *Physocarpus intermedius*, CA inhibited A549 lung, SK-OV-3 ovary, SK-MEL-3 melanoma, XF498 central nervous system, and HCT15 colon cancer cells with ED_{50} values of 4.4, 3.9, 5.1, 5.5, and 4.7 µg/ml, respectively [52]. Cytotoxicity of CA was comparable to that of ursolic acid with ED_{50} values of 4.2, 3.6, 4.6, 4.5, and 4.4 µg/ml against the same panel of cancer cells.

CA from the callus culture of *E. japonica* was cytotoxic to HSC-2 oral squamous and HSG salivary gland cancer cells with CC_{50} values of 10 and 12 µg/ml [53]. CA from the root of *Actinidia valvata* inhibited HeLa cervical cancer cells with IC_{50} values of 45, 34, and 28 µM, obtained after 24, 48, and 72 h, respectively [54]. From the leaf of *Perilla frutescens*, CA was cytotoxic to A549 lung, SK-OV-3 ovary, SK-MEL-2 melanoma, and HCT15 colon cancer cells with IC_{50} values of 10.86, 12.33, 11.65, and 10.73 µM [55]. Compared to CA, ursolic acid from *P. frutescens* exhibited stronger cytotoxic activity with IC_{50} values of 4.16, 3.82, 4.20, and 5.44 µM. The cytotoxic effect of CA, ursolic acid, and oleanolic acid against HCT116 colon cancer cells was compared [56]. Results showed that CA with an IC_{50} value of 24 µM was the most potent antiproliferative agent among the three structural analogs.

Currently, there are no studies on the structure-activity relationship of CA. Some information on ursolic acid, which is structurally similar to CA, is available [57]. For ursolic acid, the –OH group at C-3 and the –COOH group at C-28 (Fig. 1) exhibited cytotoxic activity. The C-3 configuration was important as the introduction of an amino group greatly enhanced cytotoxicity.

From the above cytotoxicity studies, CA has antitumor and antiproliferative activities against many types of human cancer cells, including some murine cancer cells. As listed in Table 1, apoptosis of cancer cells is induced through different molecular mechanisms involving mitochondrial mediation and/or caspase activation [54,56,58-62]; enhancement of sgnal transducer and activator of transcription 3 (STAT3) and/or nuclear factor-κB [63-65]; downregulation of HER2 signaling [66]; activation of AMPK or 5-FU through the inhibition of mammalian target of rapamycin [67,68]; impairment of tumor development by inhibiting the immunosuppressive activity of MDSC [69]; promotion of β-catenin degradation [70]; induction of G2/M cell cycle arrest and downregulation of phosphatidylinositol-3-kinase (PI3K)/Akt signaling [71]; disruption of maternal embryonic leucine zipper kinase-forkhead box M1 signaling [72]; activation of nuclear factor erythroid 2-related factor 2 [73]; and targeting the vascular endothelial growth factor receptor 2/steroid receptor coactivator/focal adhesion kinase pathway [74]. Inhibition of Caki renal carcinoma by CA is the only exception as cell death is non-apoptotic caused by the generation of lipid peroxidation and reactive oxygen species [75]. In addition, CA induced non-apoptotic cell death in other renal cancer cells (ACHN and A498), breast cancer cells (MDA-MB231), and hepatocellular carcinoma cells (SK-Hep1 and Huh7).

STAT3 regulates the expression of genes in response to cellular stimuli and plays a key role in cell growth and apoptosis while NF-κB transcription factors are central in immune responses [76]. The interaction between STAT3 and NF-κB signaling pathways collaboratively links inflammation to cancer. Overexpression of HER2 signaling occurs in 15–30% of breast cancer and 10–30% of gastric cancer patients [77]. Suppression of HER2 can induce cell cycle arrest and apoptosis of cancer cells. Its therapy has delayed the time of progression and increased the survival rate in patients. mTOR, a serine/threonine kinase protein, is a potential target in cancer therapy and appears to operate downstream of the PI3K/Akt pathway [78]. Apoptosis is often linked with caspase activity to bring about the demise of a cell. However, it has become apparent that cells do die even when caspase function is blocked, a process known as non-apoptotic cell death [79].

Table 1: Molecular mechanisms of corosolic acid (CA)-induced apoptosis

Cancer type (cell line)*	Molecular mechanism	Reference
HeLa cervical adenocarcinoma	Induces apoptosis through mitochondrial pathway and activation of caspases in cervical adenocarcinoma cells	[54]
HCT116 colon cancer	Induces apoptotic cell death in colon cancer cells through a caspase-dependent pathway	[56]
MG-63 osteosarcoma	Triggers mitochondria-mediated and caspase-dependent apoptosis in osteosarcoma cells	[58]
A549 lung adenocarcinoma	Induces mitochondria-mediated and caspase-dependent apoptosis in adenocarcinoma cells	[59]
HL-60, U937 and Jurkat leukemia	Exerts antiproliferative effect on leukemia cancer cells through apoptosis mediated by mitochondrial dysfunction and caspase activation	[60]
Murine colon carcinoma	Induces apoptosis in murine colon carcinoma cells, mediated by the activation of caspase-3	[61]
MG-63 osteosarcoma	Induces apoptosis of osteosarcoma cells through activating the mitochondrial pathway	[62]
T98G and U373 glioblastoma	Inhibits cell proliferation by suppressing the activation of STAT3 and NF-κB in tumor cells and associated macrophages	[63]
SK-OV3, RMG1 and ES2 ovarian carcinoma	Enhances the antitumor effects on ovarian carcinoma cells by inhibiting STAT3 and NF-κB	[64]
BCG823 gastric	Induces apoptosis of gastric cancer cells through downregulation of the NF-κB pathway	[65]
NCI-N87 gastric	Downregulates signaling of HER2 which induces cell cycle arrest and apoptosis of gastric cancer cells	[66]
SNU-601 gastric cancer	Activates AMP-activated protein kinase (AMPK) and inhibits mTOR resulting in the growth inhibition and apoptosis of gastric cancer cells	[67]
SNU-620 gastric carcinoma	Enhances the anticancer activities of 5-FU through the inhibition of mTOR in gastric carcinoma cells	[68]
Murine sarcoma	Impairs tumor growth by inhibiting the immunosuppressive activity of MDSC in tumor-bearing mice	[69]
APC-mutated colon cancer	Suppresses proliferation of mutated colon cancer cells through the promotion of β-catenin degradation	[70]
CaSki cervical cancer	Induces apoptosis, G2/M cell cycle arrest, and downregulation of PI3K/Akt signaling in cervical cancer cells	[71]
Y-79 retinoblastoma	Induces cycle arrest and cell apoptosis in retinoblastoma cells through the disruption of MELK-FoxM1 signaling	[72]
TRAMP-C1 prostate cancer	Inhibits the growth of prostate cancer cells by activating Nrf2	[73]
Huh7, HepG2, and Hep3B liver carcinoma	Inhibits migration of liver carcinoma cells by targeting the VEGFR2/Src/FAK pathway	[74]
Caki renal carcinoma	Induces non-apoptotic cell death through generation of lipid ROS in renal carcinoma cells	[75]

*All cancer types are those of human, unless stated otherwise. AMP: Adenosine monophosphate, AMPK: AMP-activated protein kinase, FAK: Focal adhesion kinase, FoxM1: Forkhead box M1, 5-FU: 5-fluorouracil, HER2: Human epidermal growth factor receptor 2, MDSC: Myeloid-derived suppressor cells, MELK: Maternal embryonic leucine zipper kinase, mTOR: Mammalian target of rapamycin, NF-kB: Nuclear factor kappa B, Nrf2: Nuclear factor erythroid 2-related factor 2, PI3K: Phosphatidylinositol3kinase, ROS: Reactive oxygen species, Src: Steroid receptor coactivator, STAT3: Signal transducer and activator of transcription 3, VEGFR2: Vascular endothelial growth factor receptor 2

CONCLUSION

This synopsis provides an update on the anticancer properties of CA, an ursane-type pentacyclic triterpene with a 30-carbon skeleton and five six-membered rings. Although *L. speciosa* (Lythraceae) remains the most important source of CA, Rosaceae and Lamiaceae are the dominant families. Studies have reported that the antitumor, antiproliferative, and apoptotic activities of CA are effective against many human cancer cell lines, including some murine cancer cells. Apoptosis involves different molecular mechanisms, and non-apoptotic cell death has also been reported. Future research on CA may focus on its structure-activity relationship, dose-response, and on the synthesis of CA derivatives with enhanced anticancer properties.

AUTHORS' CONTRIBUTIONS

This synopsis on CA and its anticancer properties stems from our earlier paper on *Lagerstroemia speciosa*, a natural remedy for diabetes. Eric Chan was responsible for the contents and finalized the manuscript. S.K. Wong downloaded relevant articles from Science Direct, PubMed, and Google Scholar databases and drafted notes for the manuscript.

COMPETING INTERESTS

The authors declare that they have no competing interests.

REFERENCES

1. Patočka J. Biologically active pentacyclic triterpenes and their current medicine signification. J Appl Biomed 2003;1:7-12.
2. Ovesná Z, Vachálková A, Horváthová K, Tóthová D. Pentacyclic triterpenoic acids: New chemoprotective compounds. Mini Rev Neoplasma 2004;51:327-33.
3. Furtado NA, Pirson L, Edelberg H, Miranda LM, Loira-Pastoriza C, Preat V, *et al*. Pentacyclic triterpene bioavailability: An overview of *in vitro* and *in vivo* studies. Molecules 2017;22:400.
4. Miura T, Takagi S, Ishida T. Management of diabetes and its complications with banaba (*Lagerstroemia speciosa* L.) and corosolic acid. Evid Based Complement Alternat Med 2012;2012:871495.
5. Stohs SJ, Miller H, Kaats GR. A review of the efficacy and safety of banaba (*Lagerstroemia speciosa* L.) and corosolic acid. Phytother Res 2012;26:317-24.
6. Garo E, Eldridge GR, Goering MG, Pulcini ED, Hamilton MA, Costerton JW, *et al*. Asiatic acid and corosolic acid enhance the susceptibility of *Pseudomonas aeruginosa* biofilms to tobramycin. Antimicrob Agents Chemother 2007;51:1813-7.
7. Yamaguchi Y, Yamada K, Yoshikawa N, Nakamura K, Haginaka J, Kunitomo M. Corosolic acid prevents oxidative stress, inflammation and hypertension in SHR/NDmcr-cp rats, a model of metabolic syndrome. Life Sci 2006;79:2474-9.
8. Kim SJ, Cha JY, Kang HS, Lee JH, Lee JY, Park JH, *et al*. Corosolic acid ameliorates acute inflammation through inhibition of IRAK-1 phosphorylation in macrophages. BMB Rep 2016;49:276-81.
9. Yang J, Leng J, Li JJ, Tang JF, Li Y, Liu BL, *et al*. Corosolic acid inhibits adipose tissue inflammation and ameliorates insulin resistance *via* AMPK activation in high-fat fed mice. Phytomedicine 2016;23:181-90.
10. Klein G, Kim K, Himmeldirk K, Cao Y, Chen X. Anti-diabetes and anti-obesity activity of *Lagerstroemia speciosa*. Evid Based Complement Alternat Med 2007;4:401-7.
11. Yamada K, Hosokawa M, Yamada C, Watanabe R, Fujimoto S, Fujiwara H, *et al*. Dietary corosolic acid ameliorates obesity and

hepatic steatosis in KK-Ay mice. Biol Pharm Bull 2008;31:651-5.
12. Chen H, Yang J, Zhang Q, Chen LH, Wang Q. Corosolic acid ameliorates atherosclerosis in apolipoprotein E-deficient mice by regulating the nuclear factor-κB signaling pathway and inhibiting monocyte chemo-attractant protein-1 expression. Circulation J 2012;76:995-1003.
13. Takagi S, Miura T, Ishihara E, Ishida T, Chinzei Y. Effect of corosolic acid on dietary hypercholesterolemia and hepatic steatosis in KK-Ay diabetic mice. Biomed Res 2010;31:213-8.
14. Shim KS, Lee SU, Ryu SY, Min YK, Kim SH. Corosolic acid stimulates osteoblast differentiation by activating transcription factors and MAP kinases. Phytother Res 2009;23:1754-8.
15. Yin MC, Lin MC, Mong MC, Lin CY. Bioavailability, distribution, and antioxidative effects of selected triterpenes in mice. J Agric Food Chem 2012;60:7697-701.
16. Al-Assaf AH. Hepatoprotective and antioxidant effect of corosolic acid on carbon tetrachloride induced hepatotoxicity. Afr J Pharm Pharmacol 2013;7:673-8.
17. Guo X, Cui R, Zhao J, Mo R, Peng L, Yan M. Corosolic acid protects hepatocytes against ethanol-induced damage by modulating mitogen-activated protein kinases and activating autophagy. Eur J Pharmacol 2016;791:578-88.
18. Fukushima M, Matsuyama F, Ueda N, Egawa K, Takemoto J, Kajimoto Y, *et al.* Effect of corosolic acid on post-challenge plasma glucose levels. Diabetes Res Clin Pract 2006;73:174-7.
19. Hou W, Li Y, Zhang Q, Wei X, Peng A, Chen L, *et al*. Triterpene acids isolated from *Lagerstroemia speciosa* leaves as α-glucosidase inhibitors. Phytother Res 2009;23:614-8.
20. Saha BK, Bhuiyan MN, Mazumder K, Haque KF. Hypoglycemic activity of *Lagerstroemia speciosa* L. extract on streptozotocin-induced diabetic rat: Underlying mechanism of action. Bangladesh J Pharmacol 2009;4:79-83.
21. Miura T, Itoh Y, Kaneko T, Ueda N, Ishida T, Fukushima M, *et al.* Corosolic acid induces GLUT4 translocation in genetically Type 2 diabetic mice. Biol Pharm Bull 2004;27:1103-5.
22. Miura T, Ueda N, Yamada K, Fukushima M, Ishida T, Kaneko T, *et al.* Antidiabetic effects of corosolic acid in KK-Ay diabetic mice. Biol Pharm Bull 2006;29:585-7.
23. Zong W, Zhao GY. Corosolic acid isolation from the leaves of *Eriobotrya japonica* showing the effects on carbohydrate metabolism and differentiation of 3T3-L1 adipocytes. Asia Pac J Clin Nutr 2007;16:346-52.
24. Shi L, Zhang W, Zhou YY, Zhang YN, Li JY, Hu LH, *et al.* Corosolic acid stimulates glucose uptake *via* enhancing insulin receptor phosphorylation. Eur J Pharmacol 2008;584:21-9.
25. Lee MS, Thuong PT. Stimulation of glucose uptake by triterpenoids from *Weigela subsessilis*. Phytother Res 2010;24:49-53.
26. Judy WV, Hari SP, Stogsdill WW, Judy JS, Naguib YM, Passwater R. Antidiabetic activity of a standardized extract (Glucosol™) from *Lagerstroemia speciosa* leaves in Type II diabetics. A dose-dependence study. J Ethnopharmacol 2003;87:115-7.
27. Tsuchibe S, Kataumi S, Mori M, Mori H. An inhibitory effect on the increase in the postprandial glucose by banaba extract capsule enriched corosolic acid. J Integr Stud Dietary Habits 2006;17:255-9.
28. Takayama H, Kitajima M, Ishizuka T, Seo S. Inventors; Tokiwa Phytochemical Co Ltd, Assignee. Process for Producing Corosolic acid. United States Patent US No. 7,071,229. 2006 Jul 4.
29. Udell RG, Hari SP. Inventors; Soft Gel Technologies Inc, Assignee. Corosolic Acid Formulation and its Application for Weight-loss Management and Blood Sugar Balance. United States Patent US No. 7,989,005. 2011 Aug 2.
30. Gokaraju GR, Gokaraju RR, Gottumukkala VS, Golakoti T, Somepalli V, Chirravuri VR. Inventors; Laila Nutraceuticals, Assignee. Structural Analogs of Corosolic Acid Having Antidiabetic and Anti-inflammatory Properties. United States Patent US No. 7,893,263. 2011 Feb 22.
31. Yoshida N, Mori C, Sasaki T. Inventors; Kenko Corp, Tokiwa Phytochemical Co Ltd, Assignee. Process for Preparing High Purity Corosolic Acid and High Purity Ursolic Acid. United States Patent US No. 8,101,795. 2012 Jan 24.
32. Kim CH, Kim JA, Song JY, Choi HJ, Inventors; Samyang Genex Corp, Assignee. Method for Production of Corosolic Acid in Suspension Culture of Plant Cells. United States Patent US No. 8,101,411. 2012 Jan 24.
33. Salvador JA, Moreira VM, Gonçalves BM, Leal AS, Jing Y. Ursane-type pentacyclic triterpenoids as useful platforms to discover anti-cancer drugs. Nat Prod Rep 2012;29:1463-79.
34. Chudzik M, Korzonek-Szlacheta I, Król W. Triterpenes as potentially cytotoxic compounds. Molecules 2015;20:1610-25.
35. Sivakumar G, Vail DR, Nair V, Medina-Bolivar F, Lay JO. Plant-based corosolic acid: Future anti-diabetic drug? Biotechnol J 2009;4:1704-11.
36. Murakami C, Myoga K, Kasai R, Ohtani K, Kurokawa T, Ishibashi S, *et al*. Screening of plant constituents for effect on glucose transport activity in Ehrlich ascites tumor cells. Chem Pharm Bull 1993;41:2129-31.
37. Ahn KS, Hahm MS, Park EJ, Lee HK, Kim IH. Corosolic acid isolated from the fruit of *Crataegus pinnatifida* var. psilosa is a protein kinase C inhibitor as well as a cytotoxic agent. Planta Med 1998;64:468-70.
38. Bai N, He KA, Roller M, Zheng B, Chen X, Shao Z, *et al*. Active compounds from *Lagerstroemia speciosa*, insulin-like glucose uptake-stimulatory/inhibitory and adipocyte differentiation-inhibitory activities in 3T3-L1 cells. J Agric Food Chem 2008;56:11668-74.
39. Huang GH, Zhan Q, Li JL, Chen C, Huang DD, Chen WS, *et al*. Chemical constituents from leaves of *Lagerstroemia speciosa* L. Biochem Syst Ecol 2013;51:109-12.
40. Chan EW, Tan LN, Wong SK. Phytochemistry and pharmacology of *Lagerstroemia speciosa*: A natural remedy for diabetes. Int J Herb Med 2014;2:100-5.
41. Meerow AW, Ayala-Silva T, Irish BM. *Lagerstroemia speciosa* 'Big Pink': An improved pink-flowered queen's crape myrtle. Hort Sci 2015;50:1593-4.
42. Thitikornpong W, Phadungcharoen T, Sukrong S. Pharmacognostic evaluations of *Lagerstroemia speciosa* leaves. J Med Plant Res 2010;5:1330-7.
43. Koshio K, Murai Y, Sanada A, Taketomi T, Yamazaki M, Kim TS, *et al*. Positive relationship between anthocyanin and corosolic acid contents in leaves of *Lagerstroemia speciosa* Pers. Trop Agric Dev 2012;56:49-52.
44. Caligiani A, Malavasi G, Palla G, Marseglia A, Tognolini M, Bruni R. A simple GC–MS method for the screening of betulinic, corosolic, maslinic, oleanolic and ursolic acid contents in commercial botanicals used as food supplement ingredients. Food Chem 2013;136:735-41.
45. Vijaykumar K, Murthy PB, Kannababu S, Syamasundar B, Subbaraju GV. Quantitative determination of corosolic acid in *Lagerstroemia speciosa* leaves, extracts and dosage forms. Int J Appl Sci Eng 2006;4:103-14.
46. Hu C, Chen L, Xin Y, Cai Q. Determination of corosolic acid in *Eriobotrya japonica* leaves by reversed-phase high performance liquid chromatography. Chin J Chromatogr 2006;24:492-4.
47. Hanahan D, Weinberg RA. Hallmarks of cancer: The next generation. Cell 2011;144:646-74.
48. Gupta M, Dahiya J, Marwaha RK, Dureja H. Therapies in cancer treatment: An overview. Int J Pharm Pharm Sci 2015;7:1-9.
49. Ren W, Qiao Z, Wang H, Zhu L, Zhang L. Flavonoids: Promising anticancer agents. Med Res Rev 2003;23:519-34.
50. Laszczyk MN. Pentacyclic triterpenes of the lupane, oleanane and ursane group as tools in cancer therapy. Plant Med 2009;75:1549-60.
51. Samad NA, Abdul AB, Abdullah R, Ibrahim TA, Rahman H, Keong YS. Zerumbone (ZER) induces apoptosis in HepG2 cells *via* mitochondrial pathway. Int J Pharm Pharm Sci 2015;7:298-302.
52. Kim YK, Yoon SK, Ryu SY. Cytotoxic triterpenes from stem bark of *Physocarpus intermedius*. Plant Med 2000;66:485-6.
53. Taniguchi S, Imayoshi Y, Kabayashi E, Takamatsu Y, Ito H, Hatano T, *et al*. Production of bioactive triterpenes by *Eriobotrya japonica* calli. Phytochemistry 2002;59:315-23.
54. Xu YM, Ge R, Du J, Xin H, Yi T, Sheng J, *et al*. Corosolic acid induces apoptosis through mitochondrial pathway and caspases activation in human cervix adenocarcinoma HeLa cells. Cancer Lett 2009;284:229-37.
55. Woo KW, Han JY, Choi SU, Kim KH, Lee KR. Triterpenes from *Perilla frutescens* var. acuta and their cytotoxic activity. Nat Prod Sci 2014;20:71-5.
56. Sung B, Kang YJ, Kim DH, Hwang SY, Lee Y, Kim M, *et al*. Corosolic acid induces apoptotic cell death in HCT116 human colon cancer cells through a caspase-dependent pathway. Int J Mol Med 2014;33:943-9.
57. Ma CM, Cai SQ, Cui JR, Wang RQ, Tu PF, Hattori M, *et al*. The cytotoxic activity of ursolic acid derivatives. Eur J Med Chem 2005;40:582-9.
58. Cai X, Zhang H, Tong D, Tan Z, Han D, Ji F, *et al*. Corosolic acid triggers mitochondria and caspase-dependent apoptotic cell death in osteosarcoma MG-63 cells. Phytother Res 2011;25:1354-61.
59. Nho KJ, Chun JM, Kim HK. Corosolic acid induces apoptotic cell death in human lung adenocarcinoma A549 cells *in vitro*. Food Chem Toxicol 2013;56:8-17.
60. Uto T, Sakamoto A, Tung NH, Fujiki T, Kishihara K, Oiso S, *et al*. Anti-proliferative activities and apoptosis induction by triterpenes derived from *Eriobotrya japonica* in human leukemia cell lines. Int J Mol Sci

2013;14:4106-20.

61. Yoo KH, Park JH, Lee DY, Hwang-Bo J, Baek NI, Chung IS. Corosolic acid exhibits anti-angiogenic and anti-lymphangiogenic effects on *in vitro* endothelial cells and on an *in vivo* CT-26 colon carcinoma animal model. Phytother Res 2015;29:714-23.
62. Jia Y, Yuan H, Shan S, Xu G, Yu J, Zhao C, *et al*. Corosolic acid inhibits the proliferation of osteosarcoma cells by inducing apoptosis. Oncol Lett 2016;12:4187-94.
63. Fujiwara Y, Komohara Y, Ikeda T, Takeya M. Corosolic acid inhibits glioblastoma cell proliferation by suppressing the activation of signal transducer and activator of transcription-3 and nuclear factor-kappa B in tumor cells and tumor-associated macrophages. Cancer Sci 2011;102:206-11.
64. Fujiwara Y, Takaishi K, Nakao J, Ikeda T, Katabuchi H, Takeya M, *et al*. Corosolic acid enhances the anti-tumor effects of chemotherapy on epithelial ovarian cancer by inhibiting signal transducer and activator of transcription 3 signaling. Oncol Lett 2013;6:1619-23.
65. Cheng QL, Li HL, Li YC, Liu ZW, Guo XH, Cheng YJ. CRA (corosolic acid) isolated from *Actinidia valvata* Dunn. Radix induces apoptosis of human gastric cancer cell line BGC823 *in vitro via* down-regulation of the NF-κB pathway. Food Chem Toxicol 2017;105:475-85.
66. Lee MS, Cha EY, Thuong PT, Kim JY, Ahn MS, Sul JY. Down-regulation of human epidermal growth factor receptor 2/neu oncogene by corosolic acid induces cell cycle arrest and apoptosis in NCI-N87 human gastric cancer cells. Biol Pharm Bull 2010;33:931-7.
67. Lee MS, Lee CM, Cha EY, Thuong PT, Bae K, Song IS, *et al*. Activation of AMP-activated protein kinase on human gastric cancer cells by apoptosis induced by corosolic acid isolated from *Weigela subsessilis*. Phytother Res 2010;24:1857-61.
68. Lee HS, Park JB, Lee MS, Cha EY, Kim JY, Sul JY. Corosolic acid enhances 5-fluorouracil-induced apoptosis against SNU-620 human gastric carcinoma cells by inhibition of mammalian target of rapamycin. Mol Med Rep 2015;2:4782-8.
69. Horlad H, Fujiwara Y, Takemura K, Ohnishi K, Ikeda T, Tsukamoto H, *et al*. Corosolic acid impairs tumor development and lung metastasis by inhibiting the immuno-suppressive activity of myeloid-derived suppressor cells. Mol Nutr Food Res 2013;57:1046-54.
70. Kim JH, Kim YH, Song GY, Kim DE, Jeong YJ, Liu KH, *et al*. Ursolic acid and its natural derivative corosolic acid suppress the proliferation of APC-mutated colon cancer cells through promotion of β-catenin degradation. Food Chem Toxicol 2014;67:87-95.
71. Xu YQ, Zhang JH, Yang XS. Corosolic acid induces potent anti-cancer effects in CaSki cervical cancer cells through the induction of apoptosis, cell cycle arrest and PI3K/Akt signaling pathway. Bangladesh J Pharmacol 2016;11:453-9.
72. Wang K, Zhu X, Yao Y, Yang M, Zhou F, Zhu L. Corosolic acid induces cell cycle arrest and cell apoptosis in human retinoblastoma Y-79 cells *via* disruption of MELK-FoxM1 signaling. Oncol Rep 2018;39:2777--86.
73. Yang J, Wu R, Li W, Gao L, Yang Y, Li P, *et al*. The triterpenoid corosolic acid blocks transformation and epigenetically reactivates Nrf2 in TRAMP-C1 prostate cells. Mol Carcinog 2018;57:512-21.
74. Ku CY, Wang YR, Lin HY, Lu SC, Lin JY. Corosolic acid inhibits hepatocellular carcinoma cell migration by targeting the VEGFR2/Src/FAK pathway. PLoS One 2015;10: e0126725.
75. Woo SM, Seo SU, Min KJ, Im SS, Nam JO, Chang JS, *et al*. Corosolic acid induces non-apoptotic cell death through generation of lipid reactive oxygen species production in human renal carcinoma Caki cells. Int J Mol Sci 2018;19:1309.
76. Fan Y, Mao R, Yang J. NF-κB and STAT3 signaling pathways collaboratively link inflammation to cancer. Protein Cell 2013;4:176-85.
77. Holla SN, Nayak V, Bairy KL, Tripathy A, Holla NS. HER-2 gene, receptors and drug target: A systematic review. Int J Pharm Pharm Sci 2016;8:4-9.
78. Bjornsti MA, Houghton PJ. The TOR pathway: A target for cancer therapy. Nat Rev Cancer 2004;4:335-48.
79. Tait SW, Green DR. Caspase-independent cell death: Leaving the set without the final cut. Oncogene 2008;27:6452-61.