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Review on Anti-Cancer and Anti-Imflammatory Activity from *Rubus coreanus* Miquel

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ABSTRACT: In accordance to the increasing number of death due to cancer and side effects of chemotherapy, attention has recently focused on combined treatment of natural component and anti-tumor agent. Therefore development of safe and effective functional substances derived from natural materials is required. The emergence of various functional activities of *Rubus coreanus* Miquel, such as antioxidant, anticancer, anti-inflammatory, etc. is continuously increasing its consumption. To utilize the above activities, many products developed by using *Rubus coreanus* Miquel extracts in the areas of foods, liquors, and cosmetics and medicines. In this review, anti-cancer, anti-inflammatory activity and patents of *Rubus coreanus* Miquel are summarized. Further studies are needed to search for development of functional material from natural origin and various application possibility using stem, leaf and fruit of *Rubus coreanus* Miquel.

Keywords: *Rubus coreanus* Miquel, anti-cancer, anti-inflammatory, patent, review

INTRODUCTION

In 2014, cancer is the number one cause of death in Korea with 28.0%, where 149 of every hundred thousand people are dying from it and the death rate from cancer is continuously increasing(Jung et al 2015). Approximately 80～90% cause for cancer, which is mainly caused by hereditary and environmental factors, is known as radiation, virus, professional carcinogen and food, smoking, drinking, and other lifestyle factors(Kleinsmith LJ 2008; Kim SS 1998). About one third of these cancer-causing factors is preventative and decreases the risk of cancer through food containing especially phytochemicals (Park EJ et al 2002). Therefore, interest in foods which have anti-cancer effects is continuously rising(Peter B, Bernard L 2008).

Furthermore, the reports of the correlation between chronic inflammation and cancer sparked continuous research on dietary intervention to decrease inflammation reaction and then the risk of cancer(Aggarwal BB et al 2006). Inflammation is suppressed by the mechanism in which the activity of nuclear factor-KB(NF-KB)is suppressed and in turn decreased the production of inflammation related factors such as nitricoxide(NO) or prostaglandin E_2 (PGE_2)(Sur YJ, Na HK 2008). The mechanism of many inflammation-suppressing substances with anti-in-

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flammatory effects is currently based on this theory(Jun YK et al 2012; Kim DH et al 2011; Lee HN et al 2011; Yoon TS et al 2010; Han JY et al 2009).

Meanwhile, the most widely used cancer treatment is surgery, which is followed by radiation therapy or chemotherapy to aid in cancer cell death (Downs-Holmes C, Silverman P 2011). However, the anti-cancer drugs used in chemotherapy are reported to not only killing cancer cells but healthy cells. They can cause side effects such as kidney toxicity, liver toxicity, hair loss, and loss of bone marrow functions, etc(Links M, Lewis C 1999; Lewis C 1994). Therefore, to decrease the anti-cancer drug side effects, a more safe and effective co-administration of natural substances is gaining attention(Xu Y et al 2012; Tokalov SV et al 2010; Cipk L et al 2003).

Rubus coreanus Miquel(*R. coreanus)*, a type of raspberry, which is a member of the Rosaceae family, which has been used as medicine since the ancient times and is known to have the most remedial effect in the berry family has been used medically since ancient times. The flower blooms in May to June and in July to August, the fruit ripens into a red color and fully ripens into a black color. The unripen fruit is what oriental medicine calls *bokbunja*(An YH, Kim YH 2007; Bae GH 2000; Jeong JS, Sin MK 1996).

R. coreanus contains as its nutrients, carbohydrates, proteins, fats and fibers(Cha HS et al 2007; Cho SH et al 2004). It is abundant in minerals such as phosphorus, iron and calcium and is especially rich in organic acids and vitamin C. Additionally, it is known to have phytochemicals, various vegetable derived bioactive components, like anthocyanin, flavonoid, tannin, quercetin and phenolic acid(Yoon I et al 2003; Kim MS et al 1997; Kim MS et al 1996; Pang KC et al 1996; Lee MW 1995; Lee YA 1995; Lee MW 1995). These substances result in *R. coreanus* to have antioxidant and antibacterial effect, anticancer and anti-inflammatory effect, anaphylaxix suppression effect, anti-angiogenesis effect, allergy related illness treatment effect, hepatitis type B (HBV) suppression effect and other various biological activity(Jeon YH et al 2009; Kim S et al 2013; Park MC et al 2007).

As biological activity of *R. coreanus* like these receive attention, consumption has continuously increase and according to National Statiscial Office research, it showed that national production area increased from 23.5 ha in 1998 to 3,368 ha in 2011 and production increased greatly from 12,282 M/T in 2008 to 17,169 M/T in 2011. However, the reality of the increase in consumption is usually in processed foods such as jam, beverages and alcoholic beverages. Therefore, there is a need for a solution search to apply it not only in processed foods but as a naturally derived biologically active substance(Choi HS et al 2006).

This study organized the research results of *R. coreanus*'s medicinal properties, especially its anticancer and anti-inflammation function. Also, it is aimed to be a base data for naturally derived biologically active substance development and application possibility search of *R. coreanus* product by analyzing existing patent application trend.

Anti-cancer Activity of Rubus coreanus Miquel

Various study results of *R. coreanus* anti-cancer effects are shown in Table 1.

To find the prostate tumor growth inhibition effects of *R. coreanus*, Baek EY et al(2009) studied to find the prostate tumor growth inhibition effects of *R. coreanus* using prostate cancer cell strain PC-3 implanted mice. All the mice were fed unripe or fully ripe fruits and their prostate tumor size significantly decrease in both groups compared to those not fed *R. coreanus*($p<0.05$). Decrease in prostate tumor is assumed to have resulted from *R. coreanus* activating caspase-3, a main gene for cell death, leading to cell death process(Baek EY et al 2013).

Additionally, Kim Y et al(2012) reported that unripe *R. coreanus* and ethanol extracts of unripe fruit (EUR) suppresses the growth of androgen-dependent LNCaP cell and androgen-independent DU145 cell. As the result of EUR administration, the expression of the proliferating tumor cell markers and cancer gene like proliferating cell nuclear antigen (PCNA) and cyclin D1 and CDK4, decreased. Its effects were greater in LNCaP, an androgen-dependent prostate cancer cell compared to androgen-independent DU145 cell. Furthermore, EUR increased pro-apoptotic protein(Bax) and decreased anti-apoptotic protein(Bcl-2, Bcl-xL) inducing mitochondria mediated cell death.

Meanwhile, Choung MG, Lim JD(2012) examined the suppressing effect of cell growth by anthocyanin fraction of *Rubus coreanus*, AFRC, in human cancer cell strains: prostate cancer, colorectal cancer, kidney and renal cancer, lung cancer, and leukemia. The results showed 50% suppression of cancer cell growth in prostate cancer cell strain(LNCaP) and lung cancer cell strain(A549) was shown at the concentration of 27.6 and 16.4 μg/mL, respectively.

On the other hand, AFRC of leukemia, colorectal cancer, and kidney and renal cancer cell strains showed cancer cell growth suppression did not occur at over approximately 500 μg/mL, thus concluding it did not have growth suppression effects. Furthermore, when AFRC was processed in normal human liver cell strain 293, growth suppression was under 5%, implying high safety and stability on normal cells. It can conclude that AFRC does not affect normal cell growth and displays high anti-cancer activity on specific cancer cell strains. Thus, it can be used in combination with existing anti-cancer drugs to assure safety and further be used as synergist to improve treatment effects.

R. coreanus extracts showed suppression effect on various cancer cells other than prostate cancer.

Kim HJ et al(2013) measured anti-cancer effect of *R. coreanus* on breast cancer cells. When treatment of ethanol extracts of *R. coreanus*, ERC, on human body breast cancer cell strain, MDA-MB-231, breast cancer cell activity showed significant decrease($p<0.05$)(0, 200, 300, 400 μg/mL) in concentration dependent manner. Also, the rate of cell death increased in concentration dependent manner by staining both Hoechst 33322 and propidium iodide ($p<0.05$). Additionally, cell death related gene expression on mRNA and protein level, death genes, Bax and caspase-3 expression significantly increased($p<0.05$) but anti-death gene, Bcl-2, expression significantly decreased($p<0.05$). It was observed that *R. coreanus* extracts not only induced decrease of breast cancer cell's activity and membrane permeability but also induced cell death by controlling gene expression contributing to cell death.

In study of Jeon SG et al(2007) *R. coreanus* extracted by methanol and each fraction(butanol fr., ethyl acetate fr., water fr.) administered in human origin stomach cancer cells, AGS and Kato3 cells, to investigate growth hindrance and DNA damage. The results showed *R. coreanus* suppressed growth activity in AGS and Kato3 cells and induced high DNA damage effects. When 100 μg/mL of buthanol fr, ethyl acetate fr. was treated in AGS, it showed high growth impediment at 77-87% and 46-60% growth impediment in Kato3. Furthermore, the result of comet assay to observe DNA damage showed *R. coreanus* extract treatment induced DNA damage in stomach cancer cells, especially in buthanol fr. It showed approximately 50% DNA damage within 1 hour of treatment.

In addition, Jeon YH et al(2009) studied if *R. coreanus* ethanol and hot water extract had cancer cell growth suppressing effect on human uterine cancer cells(HeLa) and liver cancer cells(Hep3B). In HeLa cells, of 100, 200, 400, 600, 700 μg/assay *R. coreanus* extract concentration, 700 μg/assay concentration showed high growth suppression with over 65% (ethanol extracts of *Rubus coreanus*, ERC 68.5%, hot water extract, HWE 66.4%) and Hep3B also showed high growth suppression with 67.2% and 65.8% in ERC and HWE, respectively. Therefore, the possibility of *R. coreanus* usage as anti-cancer active natural functioning material is clear.

Kim JH et al(2006) conducted *in vivo* experiment with inoculating mouse with tumor cell, Sarcoma-180, to induce ascites tumor and solid cancer and then they measured the effect of HWE of *R. coreanus* on tumor cell growth suppression. The result was *R. coreanus* showed greater cancer cell suppression effect than *dong qual*(Korean angelica root). Furthermore, when water extract of *R. coreanus* and ethanol extract of *R. coreanus* was treated in human colon cancer cell, HT-29, caspase-3 mediated cell death was induced and water extract of *R. coreanus* showed greater effects than ethanol extract of *R. coreanus*(Kim EJ et al 2005).

Meanwhile, Lee KK et al(2009) confirmed methanol extract of *R. coreanus* significantly suppressed ($p<0.05$) U937 leukemia cell growth in concentration dependent manner(1, 10, 100 μg/mL).

Anti-inflammatory Activity of Rubus coreanus Miquel

Various study results of *R. coreanus* anti-inflammatory effects are summarized in Table 2.

Lee JE et al(2013) investigated inflammation re-

Table 1. Anti-cancer activitiy of *Rubus coreanus* Miquel in experimental models

Organ	*Rubus coreanus* Miquel (RCM)	Experimental cells	Results	Ref.
Protaste	Oral dose of unripe or ripe RCM powder (2%, 10%(w/w))	Nude mice transplanted with human prostate cancer cells(PC-3)	Reduction in tumor growth by enhancing capase-3-mediated apoptotic process	Baek EY et al 2013
	50% ethanol extracts of unripe fruit of RCM	Human prostate cancer cell (DU145, LNCaP)	Reduction in proliferating cells by inducing mitochondrial-mediated apoptosis (reduced Bcl-2 & Bcl-xL, increased Bax)	Kim Y et al 2012
	Anthocyanin fraction from fruits of RCM	Human prostate cancer cell(LNCaP)	Inhibition proliferation in cells	Yoon I et al 2003
Gastric	50% methanol extracts of unripe fruit of RCM and its fraction (butanol fr., ethyl-acetate fr., water fr.)	Human gastic cancer cell (AGS, KatoIII)	Inhibition on cell growth by inducing DNA damage	Jeon SG et al 2007
Breast	30% ethanol extracts of fruits of RCM	Human breast cancer cell (MDA-MB-231)	Inhibition on cell growth by inducing apoptotic genes(Bcl-2&Bax) and enhancing capase-3-mediated apoptotic process	Kim HJ et al 2013
Colon	Aqueous and ethanol extracts of unripened fruits of RCM	Human colon cancer cell(HT-29)	Inhibition on proliferation in cells by enhancing capase-3-mediated apoptotic process	Kim EJ et al 2005
Lung	Anthocyanin fraction from fruits of RCM	Human lung cancer cell(A549)	Inhibition on proliferation in cells	Yoon I et al 2003
Uterus	Ethanol and water extracts of fruits of RCM	Human uterus cancer cell(HeLa)	Inhibition on cell growth over 60%	Jeon YH et al 2009
Liver	Ethanol and water extracts of fruits of RCM	Human liver cancer cell(Hep3B)	Inhibition on cell growth over 60%	Jeon YH et al 2009
Ascites	Oral dose of water extracts of fruits of RCM	Nude mice transplanted with sarcoma-180 cells	Inhibition on ascite tumor growth	Kim JH et al 2006
Leukocyte	Methanol extracts of ripened fruits of RCM	Human histiocytic leukemia(U937)	Induction of apoptosis expression gene : p53, NF_kB increased I_kB decreased protein: NF_kB increased PCNA,BcL-xL decreased	Lee KK et al 2009

sponse of mice peritoneal macrophage fed with unripe or fully ripe *R. coreanus* fruit intake. For 8 weeks, *R. coreanus* was fed according to concentration (unripe and fully ripe at 2% and 10%) and induced inflammatory response using lipopolysaccharide(LPS) after dividing peritoneal macrophage. Secretion of tumor necrosis factor(TNF)-α, interleukin (IL)-1β, IL-6, a proinflammatory cytokines, prostaglandin(PG)E_2,

Table 2. Anti-inflammatory activity of *Rubus coreanus* Miquel in experimental models

Rubus *coreanus* Miquel(RCM)	Experimental material	Results	Ref.
Oral dose of 2%, 10% fruits of RCM (unripened, ripened)	LPS-stimulated mouse peritoneal macrophages in mice	*Suppression of pro-inflammatory mediator expression* Reduced TNF-α, IL-β, IL-6, PGE_2 Reduced gene expression (5-LOX, IL-11, NOS-2, iNOS)	Lee JE et al 2013
Ethanol extracts of fruits of RCM (unripened, half-ripened, ripened)	LPS-stimulated RAW 264.7 murine marcrophages	*Inhibition of inflammatory mediator expression* Reduced NO, PGE_2 levels Reduced protein levels of iNOS, COX-2 Reduced production of cytokines (TNF-α, IL-6)	Yang HM et al 2008
Ethanol extracts of unripened fruits of RCM	LPS-stimulated RAW 264.7 murine marcrophages	*Activation of the HO-1pathway* Reduced NO, PGE_2 Reduced protein levels of iNOS, COX-2	Park JH et al 2006
Ethanol extracts of root and unripened fruits of RCM	LPS-stimulated RAW 264.7 murine marcrophages	*Inhibition of inflammatory mediator expression* Reduced NO, PGE_2 Reduced production of cytokines (TNF-α, IL-1β, IL-6, IL-10) Reduced mRNA levels of iNOS, COX-2	Kim SK et al 2013

and gene expression through cDNA microarray method was measured. The result showed unripe and fully ripe *R. coreanus* intake significantly suppressed TNF-α production(p<0.05) but IL-1β and IL-6 only decreased with unripe *R. coreanus* and PGE_2 secretion was not affected by either unripe or fully ripe *R. coreanus*. Also, unripe and fully ripe *R. coreanus* fruit intake markedly decreased(p<0.05) inflammatory response related gene, arachidonate 5-lipoxygenase (5-LOX), inducible nitric oxide synthase(iNOS), IL-11, expression.

According to this data, unripe and fully ripe *R. coreanus* fruit intake not only suppresses inflammatory response related gene expression, but also suppresses occurrence of chronic illnesses, especially cardiovascular related gene, ceruloplasmin, vascular endothelial growth factor(VEGF) A, tissue plasminogen activation(tPA), thrombospondin 1. It revealed effective in preventing thrombosis or various cardiovascular related illnesses. Thus, *R. coreanus* is concluded to have various application possibilities in related functional foods development.

Yang HM et al(2008)'s study compared anti-inflammatory effect of ethanol extracts depending on *R. coreanus* fruit ripening levels(unripe, medium ripe, and fully ripe). Ethanol extract of *R. coreanus* was treated after inducing inflammation on RAW 264.7 cell, a murine marcrophage, using LPS. Unripe and medium ripe fruits extracts significantly decreased nitric oxide(NO) and PGE_2 production but fully ripe fruits did not show NO and IL-6 production suppression activity.

R. coreanus has difference in phenolic compound content according to ripening level. It is reported that unripe fruit has 16 times more of cinnamic acid, 6 times more of ferulic acid and epicatechine, 4 times more of protocatechuic acid, 3 times more of gallic acid, and 2.5 times more of vanillic acid than fully ripe fruit(Kim HS et al 2011). Additionally, Park Y et al(2008) also reported that components and substance content differs by the ripened level of *R. coreanus*, which affects antioxidant effects.

Through these studies we can see ripened levels of *R. coreanus* not only affect antioxidant activities but anti-inflammatory response as well and the effects of unripe fruit is much stronger than fully ripe fruits.

Moreover, Park JH et al(2006) also reported that unripe *R. coreanus* and ethanol extracts can induce heme oxygenase-1(HO-1) expression in inflammation induced RAW 264.7 murine macrophages by LPS to suppress production of iNOS, cyclooxygenase(COX)-2, NO, and PGE_2(Elbirt KK, Bonkowsky HL 1999). Heme oxygemase(HO) is the rate-limiting enzyme in heme catabolism with consequent generation of biliverdin, free ion, and carbon monoxide(CO). Three mamalian HO isoforms have been identified, one of which, HO-1, is a stress-responsive protein endowed with important cyto-protective effects. Expression of HO-1 in marcrophages is an element of the repair processes that occur during the resolution of inflammation that leads to healing and tissue repair(Moris D, Choi AM 1968).

Additionally, it is reported that not only the fruit of *R. coreanus* but the roots also have high anti-inflammatory activity.

Kim SK et al(2013) compared anti-inflammatory activity according to different parts of *R. coreanus* with LPS induced inflammatory response RAW 264.7 cell. The cells were treated with concentration(1, 5, 10, 25, 50, 100 μg/mL) of separated polyphenol from 80% ethanol extract of *R. coreanus* roots and unripe fruit. The result showed both root extract and unripe fruit extract displayed decrease NO, pro-inflammatory cytokine(IL-1β, IL-6, IL-10), and PGE_2 production. Root extract had much stronger anti-inflammatory activity compared to the unripe fruit extract. PGE_2, especially, showed excellent reducing effect (approximately 47% when compared to NO and other inflammation factors) in the lowest concentration of 1 μg/mL of *R. coreanus* root extract. These results confirm that *R. coreanus* fruit and roots can be used as effective treatment for inflammation related diseases.

Application of Rubus coreanus Miquel

To investigate application prospect of *R. coreanus*, recent patent trend was organized and examined. Since Kwon et al(2006) presented analysis of national patent trend of *R. coreanus*, this study analyzed the patent trend after 2006.

In national patent cases, using the registered data from January 1st 2006 to September 29th, 2015 as the standard it was evident that after 2010, patent application increased significantly(Figure 1). This was due to various research results presented on *R. coreanus* and the rising interest of its application in functional foods, medicine and cosmetics. Also it seems to be related to the Korea's Ministry of Food and Drug Safety individually recognized *R. coreanus* extracts as functional raw material in December 2010. Additionally from January1st, 1990 to December 31st 2001, as there were only 2 patents applied related to *R. coreanus*, the rapid increase of interest in *R. coreanus* is evident.

Meanwhile, according to the International Patent Classification(IPC) patent registration numbers it was ranked A23(52%), A61(24%) and C12(15%) (Figure 2).

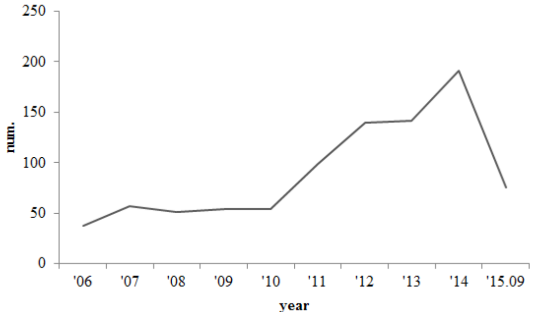

Figure 1. Number of patents related to *Rubus coreanus* Miquel from 2006 to 2015.09.

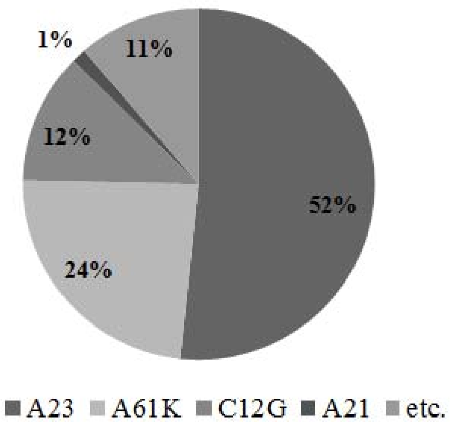

Figure 2. Classfication of *Rubus coreanus* Miquel patents according to international patent classfication (IPC) from 2006 to 2015.09.

These results were similar to patent trend from 2001 to 2006(Kwon et al 2006).

The largest portion, A23(52%), was invention pertaining 'Food and/or groceries; processing of those not included in others' including Berry juice comprising *R. coreanus* and manufacturing method thereof(application number 1020130003461), Concentrated functionality drink comprising unripened *R. coreanus* and manufacturing method thereof(application number 1020130027732), functionality drink comprising unripened *R. coreanus* and manufacturing method thereof(application number 10201300-27731), manufacturing method for *R. coreanus* tea using berry and leaf of *R. coreanus*(application number 1020070096797), etc.

The second largest portion, A61K field of 24%, was on inventions included in 'medicine and cosmetics, etc'. This field is in relation to functional product production using fixed ingredients from *R. coreanus* extracts. Typical patents include A composition comprising an extract of *R. coreanus* potentiating testosterone excretion as an active ingredient(application number 1020040114316), Composition containing an extract of *R. coreanus* for preventing and treating anxiety and depression(application number 1020060041105). Additionally, in medicinal products, patents include anticancer and anti-inflammatory effects of *R. coreanus* extracts mentioned before.

The overall of patent trend showed that A23 and A61K were the main portion and A23, 'food and groceries', held up to double the ratio of A61K, 'medicine and cosemtics, etc'. From this result, it is evident that despite its outstanding medical activity, *R. coreanus* is currently used mainly in food rather than medicine or cosmetics.

CONCLUSION

Various studies on anti-cancer, anti-inflammation effects and patents of *R. coreanus* were organized.

1. *R. coreanus* extracts displayed anti-cancer effects mostly through cancer cell growth inhibition, DNA damage induction, and cancer cell death process. And unripe fruit extract was shown to be much more effective than fully ripe fruit extract. Also, *R. coreanus* extract did not affect normal cells and only target cancer cell strains for anti-cancer activity, which implies application possibility as natural functional material to secure safety in existing anti-cancer drugs.
2. *R. coreanus* extract displayed anti-inflammatory effects by decreasing expression of inflammation related genes and inflammation mediated substances in inflammatory response induced macrophage. The ripened level of *R. coreanus* not only affects antioxidant activity but also anti-inflammatory response and effect of unripe fruit was considerable stronger than fully ripe fruit. Additionally, roots of *R. coreanus* is also reported to have high anti-inflammatory effects and thus, it can be used as an effective treating inflammation related diseases.
3. Additionally, to apply various functions of *R. coreanus*, several forms of food, cosmetics and medicine is currently being developed but food related inventions are still the mainstream.

As cancer holds a high possibility of metastasizing to various tissues, a wide-range anti-cancer therapy is commonly used. To decrease anti-cancer drug side effects whilst maintain its effectiveness, administering natural substances along with anti-cancer drug method is recently receiving much attention. Hence, continuous studies on safe and powerful natural substances are crucial.

Medicinal effects of *R. coreanus* has been widely known since antient times due to its use in oriental medicine and home remedy. Recently, through various researches, scientific effectiveness of *R. coreanus* is constantly being proven. However, medicinal effects of *R. coreanus* are considered to be effective when various ingredients are combined rather than a specific ingredient itself. Also, most research held was experimental and lacks in clinical research.

Therefore, to clearly prove usefulness of *R. coreanus* in humans, further studies on *R. coreanus* biological activity index is crucial.

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복분자딸기(*Rubus coreanus* Miquel)의 항암 및 항염 효과

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국문초록

최근 암에 의한 사망률이 증가하고, 암 치료를 위한 화학적 항암제의 부작용이 지속적으로 대두됨에 따라 암 예방뿐 아니라, 항암제의 부작용을 감소시키면서 효과는 유지시킬 수 있는 방법이 필요하다. 이를 위해 최근 천연물과 항암제의 병용투여법이 주목 받고 있으며, 보다 안전하고 효과적인 천연물질의 개발이 요구된다. 최근 복분자딸기의 항산화, 항암, 항염 등 다양한 생리활성이 부각되면서 소비가 지속적으로 증가하고 있다. 또한 이러한 생리활성을 활용하여 식품, 주류, 화장품과 의약품과 같은 분야에서 복분자딸기를 이용한 다양한 상품이 개발되고 있다. 따라서 이 고찰은 복분자딸기의 항암 및 항염증 효능에 대한 연구결과와 복분자딸기의 특허동향을 정리하였다. 향후 복분자딸기의 열매뿐 아니라, 줄기, 잎 등 다양한 부위를 활용한 천연유래 기능성 소재 개발 및 복분자딸기의 다양한 응용가능성을 모색하기 위한 더 많은 연구가 이루어져야 할 것으로 여겨진다.

주제어: 복분자딸기, 항염, 항암, 특허, 문헌고찰