

Anti-cancer and Anti-inflammatory Properties of Korean Citrus Fruits (*Citrus aurantium* L.)

Extracts in-vitro: A short review

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Abstract

Purpose. *Citrus aurantium* L.(familyRutaceae), alsoknownasbitter orange, have been used as traditional herbal medicine in many Asian countries since ancient times. Hence, the purpose of the study was to briefly discuss the new findings about anti-inflammatory and anti-cancer activities of *Citrus aurantium* L *in-vitro*.

Methods. The articles for this study were collected from pubmed and scopus electronic resources.

Results. *Citrus aurantium* L contains an abundant Flavonoids, including hesperidin, naringin and nobiletin. These Flavonoids has reported to have various medicinal benefits that include antioxidant, antimicrobial, anti-inflammatory, anticancer, anti-diabetic activities, and also used to treat cardiovascular diseases.

Conclusion. Based on the above evidence, we propose that Flavonoids from Korea *Citrus aurantium* L would be a therapeutic potential for cancer treatment and pharmacological benefit for inhibiting the inflammatory effect.

Key words: Anti-cancer effect, Anti-inflammatory effect, Citrus aurantium L, Flavonoids

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1. Introduction

In recent years, oriental herbal medicines are becoming more common and effective hence they have lesser side effects. Citrus fruits are very popular food source for their nutrient, flavor, and intrinsic attributes and commonly used as traditional medicines in several Asian countries including Korea ¹⁾. The dried, entire immature peels of citrus fruit are used in traditional herbal medicine and have demonstrated potential as a chemotherapeutic agent ^{2,3)}. *Citrus aurantium* L. is a flowering plant that belongs to the Rutaceae family of the order Sapindales, and is widely distributed in tropical and subtropical southeast regions of the world. It's also known as bitter orange, seville orange, sour orange, bigarade orange, and marmalade orange, and it also refers to a citrus tree fruit. *Citrus aurantium* L. have various bioactive compounds, such as limonoids, and polyphenols ^{4,5)}. Among these, flavonoids has reported to have various medicinal benefits that include antioxidant, antimicrobial, anti-inflammatory, and anticancer activities ^{6,7)}. The numerous studies have suggested that bitter orange supplements might be effective in treating angina ⁸⁾ and ischemic colitis ⁹⁾. In this review, we summarize these new findings and discuss the molecular mechanism of anti-inflammatory and anti-cancer activities of *C. aurantium* L *in-vitro*.

2. Flavonoids present in Korean *C. aurantium* L and its anti-cancer mechanisms

The flavonoids which present in *Citrus*

aurantium L have been used to treat cardiovascular diseases ^{5,10)}. Moreover, these flavonoids have been reported to have some properties that regulate the inflammatory response and halt carcinogenesis ¹¹⁾. The major flavonoids has been reported from *C. aurantium* L. include naringin, naringenin, narirutin, nobiletin, quercetin, kaempferol, hesperidin, neohesperidin, didymin, and poncirin ¹²⁾, and it has been listed in table 1. There are ample of evidences have showed that anti-cancer properties of Korean *Citrus aurantium* L extracts and flavonoids single compounds like cell cycle arrest and apoptosis in many cancerous cells. Park et al¹³⁾ have demonstrated that flavonoid from Korean *C. aurantium* L. could induce cell cycle arrest and apoptosis on A549 lung cancer cells through the regulation of cell cycle arrest and apoptosis-related proteins. Also, flavonoids isolated from Korea *C. aurantium* L. induced cell cycle arrest and apoptosis in AGS human gastric cancer cells ¹⁴⁾ Figure 1. Shows the overall molecular mechanism of cell cycle arrest and apoptosis of flavonoids from *C. aurantium* L. in various cancer cells. Apart from that, the citrus flavonoid hesperidin induces apoptosis in NALM-6 cells by p53 and inhibits NF- κ B activation ¹⁵⁾. And, flavonone hesperidin exhibits cytotoxic effect on human mammary carcinoma cell line MCF-7, which induces apoptosis and leads to DNA damage and, finally cell death occurs ¹⁶⁾. Moreover, Lee et al¹⁷⁾ have demonstrated that hesperidin could induce Apoptosis by inhibiting Sp1 and its regulatory protein in MSTO-211H cells. Another important flavonoid, naringin induced cell cycle arrest through p21WAF1-

Table 1. The major flavonoids reported from *C. aurantium* L.

Sl.No	Flavonoids	References
1	Naringin	Harapu et al ¹²⁾ , Park et al ¹³⁾ , Kim et al ²⁴⁾ , Lee et al ¹⁴⁾ , Kim et al ²⁵⁾
2	Hesperidin	Harapu et al ¹²⁾ , Park et al ¹³⁾ , Kim et al ²⁴⁾ , Lee et al ¹⁴⁾ , Kim et al ²⁵⁾
3	Neohesperidin	Harapu et al ¹²⁾
4	Narirutin	Harapu et al ¹²⁾
5	Naringenin	Harapu et al ¹²⁾
6	Poncirin	Harapu et al ¹²⁾ , Park et al ¹³⁾ , Lee et al ¹⁴⁾ , Kim et al ²⁵⁾
7	Isosinsetin	Park et al ¹³⁾ , Lee et al ¹⁴⁾ , Kim et al ²⁵⁾
8	Hexamethoxyflavone	Park et al ¹³⁾ , Lee et al ¹⁴⁾ , Kim et al ²⁵⁾
9	Quercetin	Harapu et al ¹²⁾
10	Sinsetin	Park et al ¹³⁾ , Lee et al ¹⁴⁾ , Kim et al ²⁵⁾
11	Hexamethoxyflavone	Park et al ¹³⁾ , Lee et al ¹⁴⁾ , Kim et al ²⁵⁾
12	Kaempferol	Harapu et al ¹²⁾
13	Tetramethyl-O-isoscutellarein	Park et al ¹³⁾ , Lee et al ¹⁴⁾ , Kim et al ²⁵⁾
14	Nobiletin	Harapu et al ¹²⁾ , Park et al ¹³⁾ , Lee et al ¹⁴⁾ , Kim et al ²⁴⁾ , Kim et al ²⁵⁾
15	Heptamethoxyflavone	Park et al ¹³⁾ , Lee et al ¹⁴⁾ , Kim et al ²⁵⁾
16	3-Hydroxynobiletin	Park et al ¹³⁾ , Lee et al ¹⁴⁾ , Kim et al ²⁵⁾
17	Tangeretin	Park et al ¹³⁾ , Lee et al ¹⁴⁾ , Kim et al ²⁵⁾
18	Hydroxypentamethoxyflavone	Park et al ¹³⁾ , Lee et al ¹⁴⁾ , Kim et al ²⁵⁾
19	Hexamethoxyflavone	Park et al ¹³⁾ , Lee et al ¹⁴⁾ , Kim et al ²⁵⁾
20	Didymin	Harapu et al ¹²⁾

Sl.No - serial number

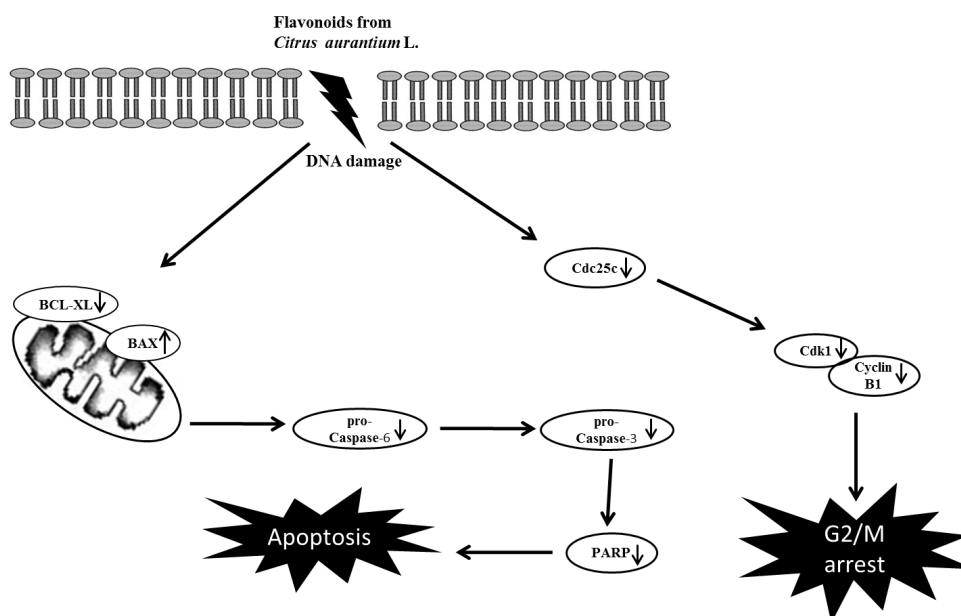


Figure 1. Pathways depicts that mechanism of flavonoids from *C. aurantium* L induced G2/M arrest and apoptosis in various cancer cells (Park et al¹³⁾ and Lee et al¹⁴⁾). Flavonoids induce G2/M arrest through the down-regulation of cdc2, cdc25c and cyclin B1 and the up-regulation of p21WAF1/CIP1. Also, it induce apoptosis through the up-regulation of the ratio of Bax/Bcl-xL, caspase 3 activity and cleaved PARP, and the down-regulation of pro- caspases (caspase-3, -6, -8 and -9) proteins (↑ - up regulation of protein and ↓ - down-regulation of proteins)

mediated Ras/Raf/ERK pathway 3,18). More recently, naringin has been exhibited mitochondria-mediated apoptosis in human cervical cancer (SiHa) cells¹⁹). Also, Arul et al²⁰) have showed that naringenin can induce cell cycle arrest and apoptosis in human hepatocellular carcinoma cells.

3. Anti-inflammatory activities of Korean *C. aurantium* L

Many studies has reported that Citrus fruits have good anti-inflammatory properties because their consumption induces antioxidant effects and decreases the risk of inflammation and blood hypertension²¹⁻²³). Recently, Kim et al²⁴) demonstrated that Korean *C. aurantium* inhibited the inflammatory response in lipopolysaccharide (LPS)-induced L6 skeletal muscle cells through the nuclear factor- κ B signaling pathway. This findings revealed the anti-inflammatory effect and mechanism (s) of action of flavonoids isolated from *C. aurantium* L. which has native to Korea and the regulation of anti-inflammation pathways in L6 skeletal muscle cells. Moreover, proteome level evidence for an interaction between flavonoids and L6 skeletal muscle cells has been showed using advanced proteome techniques like 2-DE and MALDI-TOF/MS²⁵). And also, the recent study have demonstrated that the crude methanol extract of *Citrus aurantium* L. (CME) inhibits the nuclear factor- κ B (NF- κ B) activity, and that the activation of NF- κ B is involved in cancer cell survival and proliferation²⁶).

4. Conclusions

In conclusion, many studies have demonstrated that anti-cancer and anti-inflammatory properties flavonoids from Korea *C. aurantium* L. against various cell lines in-vitro. Based on the above evidence, we propose that flavonoids from Korea *C. aurantium* L would be a therapeutic potential for cancer treatment and pharmacological benefit for inhibiting the inflammatory effect. In addition, more in vitro preclinical studies to be needed to elucidate detailed mechanisms of action in cancer cells, and be used as a potential resource of natural antioxidants for the food industry.

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