



## Formulated extract from multiple citrus peels impairs dendritic cell functions and attenuates allergic contact hypersensitivity



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### ABSTRACT

It has been reported that gold lotion (GL), a formulated product made from the peels of six citrus fruits, has many pharmacological properties, such as anti-tumor, antioxidant, and anti-inflammatory activities. In this study, we investigated the immunomodulatory effect of GL on lipopolysaccharide (LPS) stimulated mouse bone marrow-derived DC maturation and function. Our experimental results have shown that GL significantly impaired the pro-inflammatory cytokine and chemokine secretion, suppressed the expression of major histocompatibility complex class I/II and costimulatory molecules (CD40, CD80 and CD86), increased phagocytic capacity, and reduced propensity to stimulate the autologous CD4<sup>+</sup> and CD8<sup>+</sup> T cell proliferation of LPS-induced DCs. Furthermore, we found that oral administration of GL attenuated the 2,4-Dinitro-1-fluorobenzene induced contact hypersensitivity (CHS) in animal models. Subsequently, our molecular mechanism studies showed that GL interfered with LPS-induced MAPK–JNK, p38 phosphorylation and nuclear translocation of NF- $\kappa$ B p65. In an essence, these findings are the first report to provide new insight in the immunopharmacological role of GL in terms of its effects on DC.

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### 1. Introduction

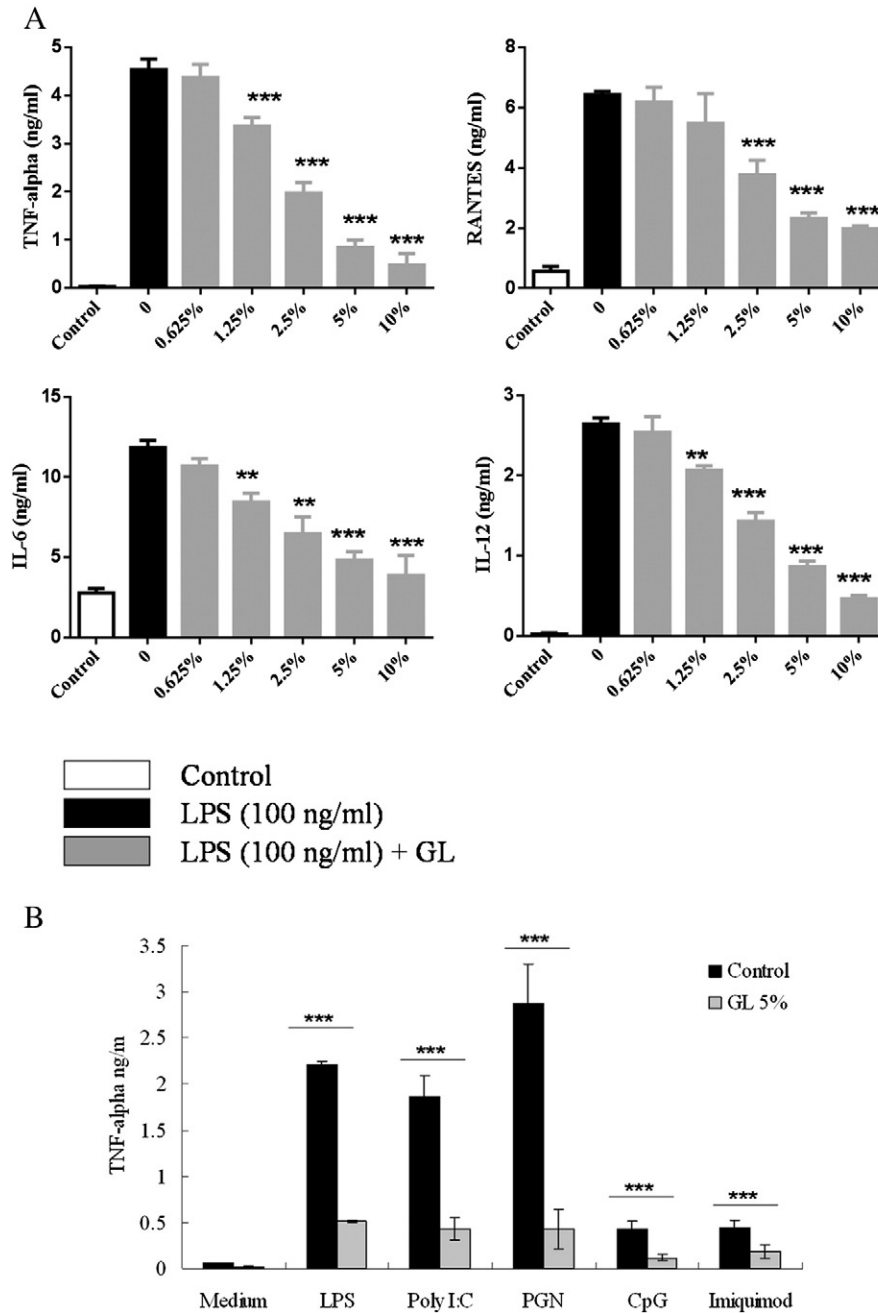
There are many types of citrus in the world, including orange, grapefruit, lemon, lime, etc. The citrus peel has drawn increased attention in recent years because it contains many special phytochemicals associated with health benefits and has the potential for development in functional foods and medicinal agents [1–4]. In oriental countries, citrus peel tinctures are often used as a medicine for phlegm and cough [5]. Recently, there have been reports to exhibit many biological properties such as anti-inflammatory, anticancer, and anti-microbial activities in vitro and in experimental animals [6–9]. In citrus fruits, the citrus peel, a rich natural source of flavonoids and polymethoxyflavones (PMFs), is of particular interest due to their broad spectrum of bioactivities. These compounds play important roles not only in biological

activities, but also in applications of food and pharmaceutical industries [10–15].

Gold lotion (GL), a formulated product made from six different citrus fruit peels (*navel oranges*, *Citrus hassaku*, *Citrus limon*, *Citrus natsudaidai*, *Citrus miyauchi* and *Satsuma*), was initially formulated in cosmetics in Japan to protect skin from ultraviolet (UV) light irradiation. Chemical analysis of GL has revealed an abundant existence of flavonoids with total content measurements of at least 450 ppm or 0.45 mg/ml. The analysis also revealed measurements of PMF content as high as 106 ppm or 0.1 mg/ml as well [16,17]. Therefore, some consumer reports indicated that topical and oral treatments of GL possess anti-cancer property against melanoma, and prostate, lung, and liver cancers. Further research from the Huntingdon Research Center in the UK found GL to be non-toxic. (Reports from Miyauchi Citrus Research Center). A recent study demonstrated the potent anti-cancer effects of citrus peel flavonoids in human prostate xenograft tumors in nude mice [18].

Evidence shows that GL has anti-inflammatory and immunomodulatory effects. Oral administration of GL protected mice against azoxymethane-induced aberrant crypt foci (ACF) in colonic tissues

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**Fig. 1.** Cytokines and chemokines released from TLR-stimulated DCs were reduced by GL. A) Immature DCs were treated with 10% GL for 1 h and then stimulated with LPS (100 ng/ml, B) or TLR ligands (including, peptidoglycan (1  $\mu$ g/ml, TLR1/TLR2), Poly:I:C (250  $\mu$ g/ml, TLR3), CpG ODN 1826 (200 nM TLR-9), and Imiquimoid (5  $\mu$ g/ml TLR-7)) for additional 18 h (TNF-alpha and RANTES for 4 h). After incubation, culture supernatants from each group were collected and subjected to ELISA for determination of the amounts of indicated cytokines. All data on the graph represents the mean  $\pm$  SD from three wells. \*\* $p < 0.01$ , \*\*\* $p < 0.001$ ; (ANOVA followed by Tukey post hoc test) versus LPS treatment alone. All results are shown as a representation of three independent experiments yielding similar result.

of mice [16], in which the protection mechanism may be involved in decreasing expression of genes associated with inflammation and tumorigenesis, such as inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2), vascular endothelial growth factor (VEGF), and matrix metalloproteinase 9 (MMP-9) in colonic tissues of mice. In addition, topical application of GL prevents 7,12-dimethylbenz[a]anthracene (DMBA)/TPA-induced skin inflammation and tumor formation [17]. Furthermore, a recent study conducted by Tadahiro et al. indicated that GL suppresses the inflammation in vitro, and exerts preventive activity through the reduced release of TNF- $\alpha$

and nitric oxide from macrophage RAW264.7 cells stimulated by LPS [19]. However, to the best of our knowledge, the cellular and molecular targets of GL in the immune system have remained unclear.

Dendritic cells (DCs) are potent antigen presenting cells that control both innate and adaptive immune systems [20]. Under steady state, immature DCs reside in the peripheral nonlymphoid tissues where they sample antigens, such as those associated with microbial pathogens and tumors, by endocytosis. Upon encountering antigens, DCs undergo the morphological, phenotypic, and functional process termed "maturation". The common characteristics of DC maturation, include the

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