Cosmeceutical Critique

Triterpenoids

Triterpenoids, to which squalene is the immediate biologic precursor, include steroids and, thus, sterols, and represent the largest group of terpenoids, the most abundant group of botanical constituents and the most common ingredient class found in volatile oils. Consequently, triterpenoids appear in numerous botanical products with traditional and modern applications to dermatology, such as *Centella asiatica* (gotu kola) and propolis.

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Indeed, the naturally occurring triterpenoids, oleanolic acid and ursolic acid, are known to confer anticarcinogenic and anti-inflammatory effects in certain cells (Exp. Dermatol. 2006;15:66-73). Ursolic acid and the natural triterpenoid erythrodiol have also been found to be effective in a multiple-dose 12-*O*-tetradecanoylphorbol-13-acetate (TPA) model of chronic dermal inflammation (Eur. J. Pharmacol. 1997;334:103-5).

Although triterpenoids are not as prevalent in as many of the highly touted herbal sources as polyphenols, this group of compounds is gaining increased attention for its anti-inflammatory and anti–tumor-promoting activity. In one trial, investigators studying the triterpenoids oleanolic acid and ursolic acid found that the former induced the differentiation of keratinocytes through peroxisome proliferator–activated receptor (PPAR)–α activation. In addition, topical application of oleanolic acid improved the recovery of epidermal permeability barrier function and increased ceramides in epidermis (Exp. Dermatol. 2006;15:66-73).

The preponderance of data on triterpenoids, though, points to the anti–tumor-promoting capacity of this copious botanical class of compounds.

Anti–Tumor-Promoting Actions

In a study designed to identify potential anti-tumor promoters, investigators screened 21 cucurbitane triterpenoids using an in vitro assay system, and found that several of the compounds significantly inhibited Epstein-Barr virus (EBV) activation induced by the tumor promoter TPA.

These compounds were scandenoside R6, 23,24-dihydrocucurbitacin F, 25-acetyl-23,24-dihydrocucurbitacin F, 2-*O*-beta-D-glucopyranosyl-23,24-dihydrocucurbitacin F, and cucurbitacin F. Two triterpenoids, 23,24-dihydrocucurbitacin F and 2-*O*-beta-D-glucopyranosyl-23,24-dihydrocucurbitacin F, also displayed significant activity against skin tumor promotion in an in vivo two-stage murine carcinogenesis model (Biol. Pharm. Bull. 1994;17:668-71).

A later in vitro study conducted by the same lab to identify anti–tumor promoters considered 23 triterpenoid hydrocarbons isolated from ferns. Significant inhibitory activity against EBV induced by TPA was exhibited by hop-17(21)-ene, neohop-13(18)-ene, neohop-12-ene, taraxerane, multiflor-9(11)-ene, multiflor-8-ene, glutin-5(10)-ene, and taraxastane. In a two-stage in vivo murine carcinogenesis model using 7,12-dimethylbenz[*a*]anthracene (DMBA) for initiation and TPA for promotion, hop-17(21)-ene and neohop-13(18)-ene displayed significant anti–tumor promoting effects on mouse skin (Biol. Pharm. Bull. 1996;19:962-5).

Three years later, some of the same investigators, studying triterpenoids derived from *Taraxacum japonicum* (Compositae) roots, found that taraxasterol and taraxerol significantly inhibited the effects of TPA-induced Epstein-Barr virus early antigen (EBV-EA) induction, which is a preliminary in vitro screening approach to identifying anti–tumor-promoting agents. These compounds also exhibited potent anti–tumor-promoting activity in the two-stage murine skin carcinogenesis model initiated by DMBA and promoted by TPA (Biol. Pharm. Bull. 1999;22:606-10).

In a study from Osaka (Japan) University of Pharmaceutical Sciences, seven serratane-type triterpenoids isolated from different *Picea* species all exhibited potent inhibitory effects on EBV-EA activation induced by TPA, and did so more strongly than oleanolic acid. In addition, 13alpha,14alpha-epoxy-3beta-methoxyserratan-21beta-ol displayed significant anti–tumor-promoting activity in the in vivo two-stage murine carcinogenesis model (Cancer Lett. 2001;172:119-26).

The same lab subsequently studied 11 serratane-type triterpenoids isolated from various *Picea* species and three synthetic analogues for their potential inhibitory effects on EBV-EA activation induced by TPA. That study yielded more corroborative findings, as several of the compounds showed potent inhibitory activity, again more strongly than the oleanolic control, including 21-episerratenediol, serratenediol, diepiserratenediol, 3-beta-hydroxyserrat-14-en-21-one, and 3-alpha-methoxy-21-beta-hydroxyserrat-14-en-16-one. Furthermore, no cytotoxicity was associated with these compounds.

Of these triterpenoids, 21-episerratenediol was found to demonstrate significant inhibitory effects on skin tumor promotion in the in vivo two-stage mouse skin carcinogenesis model using DMBA for initiation and TPA for promotion. The investigators suggested that the triterpenoid 21-episerratenediol has potential as an effective cancer chemopreventive agent (Cancer Lett. 2003;196:121-6).

In a separate experiment conducted by this lab, two new serratane-type triterpenoids, 3beta-methoxyserrat-13-en-21-beta-ol and 13-beta,14beta-epoxy-3beta-methoxyserratan-21beta-ol, also isolated from *Picea* plants, exhibited strong anti–tumor-promoting effects on mouse skin carcinogenesis (Planta Med. 2003;69:1041-7).

This lab also showed that, in a test of the lupane-type triterpenoids isolated from the stem bark of *Glochidion zeylanicum* as well as synthetic analogues, glochidiol and lup-20(29)-ene-1beta,3beta-diol were the strongest inhibitors of EBV-EA activation induced by TPA. Glochidiol also exhibited the greatest inhibitory effect on skin tumor promotion (Planta Med. 2004;70:1234-6).

Other Anticarcinogenic Actions

In 2005, investigators at the University of North Carolina, Chapel Hill, published a report on cimigenol, an acid- and base-stable triterpenoid found in species such as *Cimicifuga racemosa*, *C. dahurica*, and *C. japonica*. These researchers had previously shown that cimigenol and some of its derivatives had strong inhibitory effects on mouse skin tumor promotion induced by TPA in a two-stage carcinogenesis test. Continuing that previous work, the investigators repeated screens of cimigenol and also tested 15 related compounds as potential anti-tumor promoters by using the in vitro, short-term TPA-induced EBV-EA activation assay (Bioorg. Med. Chem. 2005;13:1403-8).

Of these compounds, the researchers found that cimigenol-3,15-dione showed the greatest potency and, in a subsequent two-stage DMBA/TPA carcinogenesis assay, reduced, at 20 weeks, the number of papillomas per mouse to 48% of controls. Both cimigenol and cimigenol-3,15-dione were also nearly as potent as epigallocatechin gallate, a primary constituent of green tea, in terms of anti-tumor initiation activity, as demonstrated in a two-stage carcinogenesis assay of mouse skin tumors induced by peroxynitrite (initiator) and TPA (promoter).

The investigators concluded that these two triterpenoids amply demonstrate anti-tumor promotion as well as anti-tumor initiation and warrant consideration as significant cancer chemopreventive agents (Bioorg. Med. Chem. 2005;13:1403-8).

Protection Against UV

Four triterpenoids isolated from the stems of *Styrax japonica* were recently found to significantly inhibit matrix metalloproteinase-1 (MMP-1) in primary human skin fibroblasts induced by UV radiation. This finding is significant given the association between the upregulation of MMPs and chronic skin damage (Biol. Pharm. Bull. 2005;28:2003-6).

Previously, some of the same investigators studied the effects of 3,23-dihydroxy-20(29)-lupen-27-oic acid, a triterpenoid derived from *Tiarella polyphylla*, on the regulation of MMP-1 and type 1 procollagen in UV irradiation of cultured old-age human dermal fibroblasts. The triterpenoid dose-dependently induced regulation of type 1 procollagen and diminished regulation of MMP-1 at the protein level (Arch. Pharm. Res. 2004;27:1060-4).

Other Pharmacologic Actions

Triterpenoids also have been found in *Boswellia serrata*, an herb used in traditional medicine to treat inflammatory and arthritic conditions (and discussed in this column in November 2006, p. 17).

In a study published in 2000, the primary components and derivatives of *Boswellia* markedly inhibited TPA-induced increases in skin inflammation, epidermal proliferation, the number of epidermal cell layers, and tumor promotion in DMBA-initiated mice. DNA synthesis in human leukemia HL-60 cells was also shown to be inhibited by the addition of various forms of boswellic acid. The investigators suggest that such findings demonstrate the anticarcinogenic and antitumor properties of the major constituents, including triterpenoids, of this herb (Biofactors 2000;13:225-30).

The anti-inflammatory activity of several triterpenoids suggests the potential for numerous additional medical applications. A study evaluating the mechanism of anti-inflammatory activity displayed by triterpenoids on edema induced in mouse ears and paws, as well as rat skin, revealed that the inhibition of protein kinase C may play a crucial role in facilitating the anti-inflammatory activity of this class of compounds (Eur. J. Pharmacol. 2000;410:69-81).

In another study, several triterpene constituents of *Vochysia pacifica* Cuatrec, a South American tree used by traditional communities to treat inflammation, skin sores, asthma, and pulmonary congestion, were found to exert mild inhibitory activity on the intracellular target for new anti-inflammatory medications, namely the cAMP phosphodiesterase 4 isozyme (PDE4) (Phytother. Res. 2005;19:75-7).

Some triterpenoids have been documented as irritating (J. Asian Nat. Prod. Res. 2003;5:35-41) and others as toxic, which is not unexpected as these compounds comprise the primary constituent class in the volatile oils of plants. Given the breadth of this biochemical class, it is expected that some members would be toxic and others safe and beneficial to human health, such as the triterpenoid saponin glycyrrhizin, derived from licorice root (and featured in this column in March 2007, p. 24, and April 2007, p. 30). Triterpenoid saponins, or sapogenins, are used in some emulsifiers, including some Estée Lauder products, for their capacity to confer antifungal, anti-inflammatory, antimicrobial, and adaptogenic activity.

Conclusion

As we continue to explore botanical sources for medical and cosmetic purposes, we will learn more about the numerous triterpenoids found in plants. This class of biochemical compounds typically receives less attention than polyphenols in discussions of the most potent herbal ingredients used in dermatology, but the considerable potential of triterpenoids to be used in a broad range of cutaneous applications is gradually becoming appreciated. ■

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