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An insight review on andrographolide from the king of bitters and its therapeutic potential for skin cancer and cosmeceutical applications

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Abstract

Global skin cancer incidence is rising significantly; and can potentially become life-threatening by metastatic spread. Multiple treatment options are available but suffer from dose limiting toxicity. Andrographolide, a bioactive molecule from *Andrographis paniculata*, is an alternative/traditional solution for skin cancers with additional benefit of skin lightening. Andrographolide has significant anticancer activity involving multiple mechanisms such as inhibition of COX-2 expression, inactivation of p300 signaling and VEGF pathway, inhibition of Hh pathway, cellcycle arrest at G1/S phase, inhibition of iNOS expression, *etc*., with a safety profile. The current review focuses on promising applications of andrographolide for different skin and cosmetic problems. This is the first comprehensive review highlighting the dermal applications of andrographolide with special emphasis on its delivery for cosmeceutical usage.

1. Introduction

Skin-related complications are becoming common due to exposure of UV rays, genetic and unknown reasons. Melanoma and non-melanoma are the commonly observed types of skin cancers. Treatment involves expensive surgery which is sometimes contraindicated, owing to comorbidities or rising cosmetic expectations (Sadegh *et al.*, 2010). Non-surgical treatments suffer from critical side effects such as local pain, swelling, and erythema. Perilesional injections of PEG inter leukin produce flu like symptoms (Kaplan *et al.*, 2000) and topical creams like imiquimod and fluorouracil usage suffer from adverse effects and lower clearance rates. Natural products play a versatile role because side effects are minimal. *Andrographis paniculata* (Burm. f) Nees (Acanthaceae family) known as “king of bitters” (Okhuarobo *et al.*, 2014) is enriched with various bioactives like andrographolide, 14-deoxyandrographolide, 14-deoxy-11, 12-didehydroandrographolide, neoandrographolide, isoandrographolide, 14-deoxyandrographolide-19-β-D-glucoside, homoandrographolide, andrographolide graphan, andrographolide graphosterin, and stigmasterol, along with newly discovered enzymes (Shailaja *et al.*, 2018) and proteins (Srinath *et al.*, 2017) by *in silco* modelling. Andrographolide (AGD) is apotent molecule, inhibits different skin cancers by multiple mechanisms (Tan *et al.*, 2016). Gorter (Bright *et al.*, 2001) in 1911, isolated the pure crystalline molecule of AGD with a major role in allopathic, Ayurveda, and herbal formulations. AGD is a constituent in 26 Ayurveda formulations (Kumar *et al.*, 2014) and is called the natural antibiotic (Patil and Jain, 2021) on account of a plethora of applications including anti-bacterial (Lulu Zhang *et al.*, 2020), antiviral (Gupta *et al.*, 2017; Latif *et al.*, 2020), anti-inflammatory (Duan *et al.*,2019; Burgos *et al.*, 2020), antidepressant (Zhang *et al.*, 2019), anti-hyperglycemic (Su *et al.*, 2020) anticancer (Islam *et al.*, 2018), neuro protective (Lu *et al.*, 2019), cardioprotective (Lin *et al.*, 2020; Xie *et al.*, 2020) activities. AGD is potentially useful in parkinsonism (Ahmed *et al.*, 2021; Geng *et al.*, 2019) skeletal muscle regeneration (Wu *et al.*, 2020), osteosarcoma (Shengdong *et al.*, 2020), gastric vascular homeostasis (Yao *et al.*, 2019), ulcerative colitis (Liuhong Zhang *et al.*, 2020), COVID-19 therapy (Shi *et al.*, 2020), hepatic injury (Wang *et al.*, 2019), pulmonary fibrosis (Karkale *et al.*, 2018), against infections caused by Zika, Dengue virus (Li *et al.*, n.d.) and Chikungunya virus (Wintachai *et al.*, 2015), suppression of melanin synthesis (Zhu *et al.*, 2015).

There is a rapid spread of skin cancer globally because of exposure to sunlight (UV rays) (Zeinali *et al.*, 2021), life style changes and mutations. Malignant melanoma and non-melanoma are two types of skin cancers, where malignant melanoma occurs due to mutations in skin melanocytes, starting from a single mole. Non-melanoma (NMSC) originates from the epidermal layer (Padya *et al.*, 2021). In rare cases, skin cancer even leads to death, necessitating timely treatment. The current review addresses the role of AGD in skin cancer and its skin lightening properties. Although, AGD is potentially useful in multiple cancers through different mechanisms; there is dearth of an extensive review on topical applications of AGD,

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exploring various applications of AGD and its derivatives in dermal therapies. As AGD contains interesting molecular properties with versatile activities, it gave an impetus to the researchers to evaluate the efficacy of AGD and its derivatives against different activities.

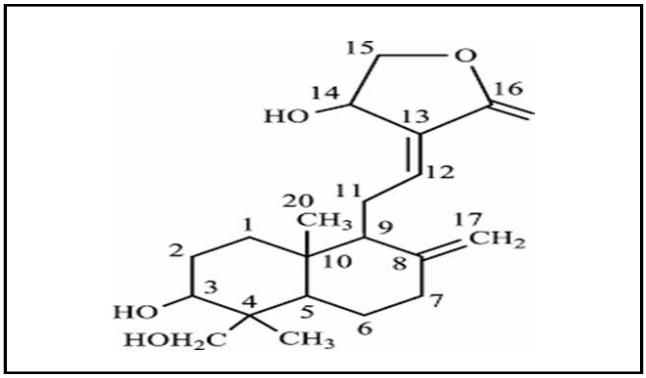

Figure 1: Structure of AGD.

2. Materials and Methods

Detailed literature survey was done by different databases of various scientific platforms like Pubmed, Pubchem, science direct, Sci-finder scopus, Google scholar and reports have been explored with various key words to gain the knowledge for writing this review article. By the use of various keywords like andrographolide, andrographis, kalmegh, skin lightening, anticancer, basal cell cancer, skin cancer, melanoma. Many articles were found, out of which 37 articles are mainly reviewed to include under introduction and the rest of the articles are utilized and reviewed for all the other sections.

3. Healthy skin vs cancerous skin

To have critical idea about various treatments against skin cancer, the knowledge about the morphology of skin cancer along with the basic structural aspects of healthy skin will help to understand different mechanisms and pathways of skin cancer. Healthy skin possesses a pH of 7.4, whereas cancerous skin (melanoma tissue) contains a pH range of 5.5-6.5 due to the presence of lactic acid.

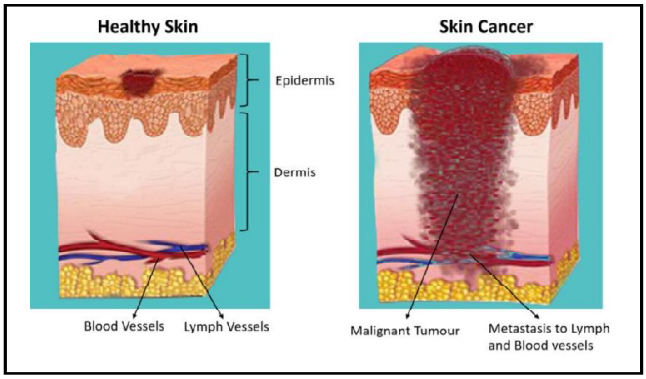

Figure 2: Healthy skin VS cancer skin (Frank, 2016).

Eventual UV exposure leads to the development of basal cell carcinoma (BCC), whereas SCC occurs due to chronic UV exposure ("Skin Cancer Foundation," n.d.). Merkel cells are named as touch receptors, located deep in the top layer of the skin as they are responsible for sensation by connecting with the nerves (Ramahi *et al.*, 2013). The tumors associated with these cells are mainly due to sun exposure (Marullo *et al.*, 2004). Merkel skin cancer grows with high speed and appears as skin /red/bluish-red/purple pearly pimples (Schadendorf *et al.*, 2017). Kaposi sarcoma is a type of cancer where patches of abnormal tissue growth are observed under the skin (MacGill *et al.*, 2018). These patches or lesions are usually red or purple (Cesarman *et al.*, 2019) consistsof cancer cells, blood vessels and blood cells. Dermato fibrosarcoma is a rare cutaneous neoplasm with an incidence rate of 0.8 to 5 per 1 million people in an year (Lyu *et al.*, 2018) with a high recurrence rate, where it is observed in people at an age of 30-50 years. Surgical excision is the standard treatment.

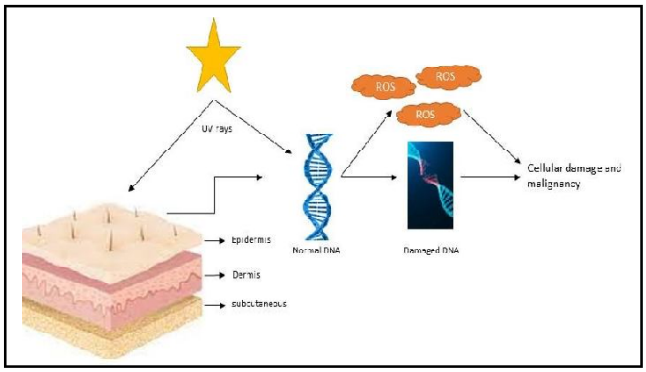

Figure 3: Pathophysiology of skin due to UV rays exposure (Uraiwan Panich, 2015).

4. Potential of andrographolide as a model anticancer agent

From ancient times to the present, AGD has become a well-recognized molecule of interest for various ailments and disorders. Especially, it had proved its efficacy against various cancers through different mechanisms.

4.1 Effect on breast cancer

At 10 μM, and 20 μM concentrations, AGD produced 20% and 50% inhibition of MDA-MB-231 cells (breast cancer cells), demonstrating its ability to suppress breast cancer growth and tumor angiogenesis by inhibiting COX-2 expression (both protein and mRNA) *via* inactivation of p300 signaling and VEGF pathway (Peng *et al.*, 2018).

4.2 Effect on prostate cancer

Flow cytometry has confirmed that, AGD inhibits PC3 (prostatic small cell carcinoma) cell proliferation at 25 μM, with the inhibition of cell cycle progression. AGD at 10 mg/kg plays an active role against prostate cancer progression, by inducing DNA damage in cancer cells, on SCID mice (Forestier-román *et al.*, 2019).

4.3 Effect on colon cancer

AGD inhibits the rapid stimulation of hedgehog signaling pathway (Hh) in colon cancer. In HCT-116 cells, AGD demonstrated dose and time dependent anti-proliferative effect in colon cancer *via* inhibition of Hh pathway by down regulating Smo and Gli1 genes (Khan *et al.*,2020). While 5-Fluoro uracil (5-FU) is effective only in 10% on advanced colorectal cancer (CRC), a combination of AGD and melatonin (MLT) synergistically enhanced the individual potencies of the compounds against the inhibition of colorectal cancer, where the decreased viabilityof HT-29 and HCT-15 mCRC cells were observed due to induction of ER stress proteins along with suppression of angiogenesis (Banerjee *et al.*, 2021).

4.4 Effect on hepatoma cancer

AGD has inhibited the growth of hepatoma tumor at 10 mg/kg, by reduced VEGFD expression *via* inducing c-fos protein degradation (Ji *et al*., 2015).

4.5 Effect on cervical cancer

Inducible nitric oxide synthase (iNOS) is over expressed in cervical cancer. AGD has shown a significant apoptotic effect on cervical cancer cells *via* stimulated cell cycle arrest at G1/S phase, along with the inhibition of iNOS expression (Pasha *et al.*, 2021).

5. Status of *A. paniculata* and AGD on clinical trials

Totally, 20 clinical trials were conducted on *A. paniculata* to the patients, suffering from various ailments such as, multiple sclerosis, colorectal neoplasms, tonsillitis, bronchitis, squamous cell carcinoma, osteo arthritis, migraine and COVID-19. In the current review, more emphasis been given to anticancer studies of andrographis, which was tested against palliative management of advanced esophageal cancer. 30 patients are recruited for the clinical trial of granules of *A. paniculata*, manufactured by Nong's Company Limited as per GMP standards.

Table 1 : Clinical trial data of AGD (Philip W.Y. Chiu, 2021)

Sl.No.	Study title	Conditions	Phase	Status
1.	*Andrographis paniculata* (AP) effect on palliative management of advanced esophageal cancer	Squamous cell carcinoma of esophagus	Phase III	Recruiting

6. Andrographolide an effective bioactive entity against dermal cancer

The current section illustrates the effect of andrographolide against various dermal cancers through inhibition of various mechanisms and pathways.

6.1 Effect of AGD against melanoma

AGD at a dose of 0.1 and 0.25 µg/ml, in B16F-10 cells produced cell shrinkage, DNA fragmentation, membrane blebbing and appearance of apoptotic bodies, possibly initiated by proapoptotic signaling pathways such as NF-κB-induced Bcl-2-mediated survival signaling, and p53-induced caspase-3 signaling (Pratheesh Kumar *et al*., 2012). AGD also exhibits tumor-specific angiogenesis by regulating pro and antiangiogenic factors such as IL-2, VEGF, nitricoxide, TIMP-1 and other pro-inflammatory cytokines (Sheeja *et al.*, 2007).

6.2 Study of andrographolide in pharmacokinetic models

The *in vivo* study to predict the effect of AGD against melanoma was carried out using xeno graft/syngenic tumor models. AGD is a versatile pharmacophore against B16F0 melanoma cells by inducing p27, down regulating cyclin-dependent kinase 4 (CDK4), and increasing interleukin-2, tumor necrosis factor (Rajagopal *et al.*, 2003).

6.3 Effect of AGD on non-melanoma skin cancer cells

AGD and AGD loaded nano emulsions (AGD-NE) have not shown any toxic effects to normal skin fibroblasts present in healthy skin. AGD-NE inhibits non-melanoma cancer by apoptotic induction of A-431 cells with IC_{50} of 54.80 µg/ml (Sooksai *et al.*, 2019).

6.4 Effect of AGD on human skin cancer

B16 cells are murine tumor cell lines, used in the investigation of metastasis and solid tumor formation in human skin cancer research. Subcutaneous inoculation of B16 cells in C57BL/6 mice administered with oral AGD drop pills at a dose of 0.143 µg/20 g reduced tumor volume, weight and prolonged survival time. AGD was remarkably effective against tumor-induced mice, by suppressing B16 cells proliferation (HE Xiao-dong *et al.*, 2011). AGD induced apoptosis *via* G2/M phase arrest by activating p38 signaling pathway on human malignant A375 cells, which have been confirmed by flow cytometry and annexing V/PI staining studies, evidential increase in expression of cleaved- PARP and caspase 3, demonstrating potential in malignant melanoma (Liu *et al.*, 2018).

7. Cosmetic applications of andrographolide

0.1-0.2 % of AGD can inhibit endothelin-1(ET-1), which plays a major role in the proliferation of melanocytes during melanogenesis (process for melanin formation). AGD helps lighten the skin by inhibiting of (ET-1). AGD also increases superoxide dismutase (SOD) and catalase, thereby inhibiting the release of ROS, modulation of NO levels, facilitating vasoconstriction that makes AGD useful in formulations for under-eye darkness (Andrographolide, n.d.). The skin flap is used to reconstruct the damaged tissue by the transfer of healthy skin tissue from one location to another. However, insufficient blood flow can cause flap necrosis in multiple cases. AGD application decreases oxidative stress, inhibits apoptosis, thereby boosting autophagy that improves skin flap survival (Jiang *et al.*, 2021). Human dermal fibroblasts are the main components in the dermal sheet of the skin, where they maintain skin health. AGD is a potential natural ingredient to f interest in the cosmetic industry against ageing and in skin care. AGD (5 µg/ml) decreases IL-6 production and TNF-α expression in human dermal fibroblasts (HDFa) (Mussard *et al.*, 2020). Epidermal melasmais one of the disorders associated with hyper pigmentation, where dark patches on the face, especially in young women exposed to UV rays or suffering from hormonal imbalance, *etc*., AGD gel in combination with glabridin and apolacto ferrin improves epidermal melasma (Cantelli *et al.*, 2020). Chitosan -HA composite AGD-loaded lipid nanoparticles showed better wound healing property with a controlled drug release of 72 h, when compared to the control (Sanad *et al.*, 2017). AGD is useful in hyper pigmentation disorders, because it controls melanin production by inhibiting TYR activity and down regulating MITF genes, which decreases phosphorylation of GSK 3 β dependent on Akt (Zhu *et al.*, 2015). ASB (3.6 mg) in mouse increased skin collagen content by 53% and decreased epidermal thickness by 43%. UV-irradiated mice could diminish damage of collagen and elastic fibres along with down-regulation of mediators like TNF-αc IL-1β, IL-6, IL-10 (Zhan *et al.*, 2016). Anti-acne skin care compositions typically employ andrographis extract, *Radix salviae* miltiorrhizae extract and thiocticacid. A composition containing *A. paniculata* extract and AGD induces secretion of a

growth factor from stem cells and skin cells, which promotes cell proliferation by improvement of skin wrinkles, inhibition of skin ageing, improvement of skin elasticity, skin regeneration, or improvement of wounds or scars formed on the epidermis (L *et al*., 2014).

8. Rationality in designing of andrographolide delivery for dermal care

Emulgels are mainly meant to incorporate the drugs with poor water solubility and better penetration capacity (Choudhury *et al*., 2017). Andrographolide is insoluble in water and belongs to BCS class II, with a log *p* value of 1.96260, where its properties are absolutely suitable to design a topical formulation (Asasutjarit *et al.*, 2021) has formulated the nanoemulsion of andrographolide and evaluated its potential against topical studies with promisable results, which has proved the ability of this pharmacophore against skin cancer as well as for skin lightening purpose. Phytomedicines are gaining attention, with minimum side effects and maximum efficacy (Parveen *et al.*, 2020). This gave an impetus to design formulation of andrographolide as an emulgel with better delivery approach for topical route.

9. Conclusion

AGD is a model molecule among natural products with multiple biological roles against numerous cancers operating through different mechanisms. AGD has a good safety profile. Bioavailability of AGD in various dosage forms demonstrate efficacy against various cancers. Working through a variety of pathways, AGD is not only useful against dermal cancers, but also as a skin-lightening and anti-ageing agent. AGD may be considered as a safe dermal and cosmeceutical agent.

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Conflict of interest

The authors declare no conflicts of interest relevant to this article.

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