Prayogik Rasayan

Erythrodiol, an Oleanane-type Triterpenoid: Natural Resources and Medicinal importance

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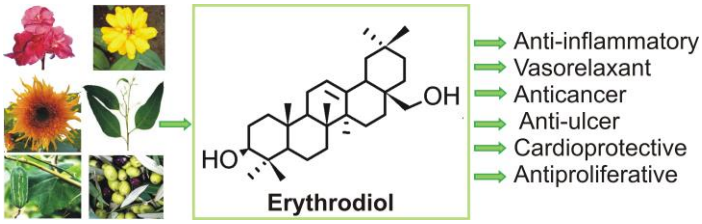
Erythrodiol, is a naturally abundant biologically active triterpenoid. It is the biosynthetic precursor of pentacyclic oleanae-type triterpenic acids in plants. The molecule has a β-amyrin type fused pentacyclic (6-6-6-6-6) carbon skeleton and two hydroxyl groups (–OH) which are attached at the two opposite ends of the rigid triterpenoid moiety. The molecule also has an endo-cyclic "C=C" connecting C12 and C13. Herein, we have reviewed the various plant resources of this oleanane-type triterpenoid erythrodiol. Various pharamacological activities of erythrodiol have also been discussed.



Keywords: Erythrodiol, natural resource, biological activity

1. Introduction

Terpenoids are a class of plant secondary metabolites containing a multiple of isoprene (C5) units.[1,2] Terpenoids are biosynthesized in various parts of a plants via different enzymatic pathway for their own defense or attracting pollinators.[3] Depending upon the biosynthesis process terpenoids are acyclic to polycyclic in nature and having the length in nanometric dimension. Depending upon the number of carbon atoms present; they may be mono- (C10), sesqui- (C15), di- (C20), sesqua- (C25), tri- (C30), sester- (C35) and tetra- (C40) terpenoids.[4] Terpenoids have drawn potential research interest during the past decade due to their : (i) renewable nature, (ii) biocompatiability, (iii) diversified structural features, (iv) pharamacological activities, (v) interesting self-assembly properties, etc.[5,6,7,8,9] In plants most of the triterpenoids remain either in free form or as aglycon in naturally occurring saponins linked with sugars. Erythrodiol (3β-olean-12-ene-3, 28-diol) is a β-amyirn type pentacyclic dihydroxy triterpenoid having the molecular foruma $C_{30}H_{50}O_2$. In plants it is the precursor of other oleanane-type triterpenic acids like oleanolic and maslinic acids. In this article various plant sources (Figure 1) and pharamocological activities (Figure 2- 5) of erythrodiol have been discussed.

2. Natural Resources of erythrodiol

Plants are rich in many kinds of phytochemicals like terpenoids, flavonoids, carotinoids, fatty acids, polyphelos etc.[10] Triterpenoids (C30), a class of secondary metabolites are found in plenty in many plants. Literature survey reveals that erythrodiol **1** ($C_{30}H_{50}O_2$), an oleanane-type trierpenoid is present in different parts such as leaves, bark, fruit, flower, seed, etc. of many plants. J. E. Orr *et al* isolated **1** from *Arctostaphylos Uva Ursi* (Linn) in 1945.[11] Carl Djerassi and co-workers isolated erythrodiol from a Guatemalan cactus *Lemaireocereus longispinus* in the year 1953.[12] K. Strüby and co-werkers isolated **1** from *Helianthus annuus*[13] (sunflower) in 1972. G.S. Saharia *et. al* isolated **1** from *Acacia senega*[14] in 1981. J. G. Tous *et. al* isolated **1** from vegetable oils in 1986.[15] T. Akihisa and co-workers isolated **1** from the seeds of *Coccinia grandis*[16] (ivy gourd) fruit in the year 1997. R. Mata *et. al* isolated **1** from *Conyza filaginoides*[17] in 1997. G. G.Santos *et. al* isolated **1** from *Eucalyptus globulus*[18] in 1997. D. K. Kim *et. al* isolated **1** from *Ilex macropoda*[19] in 2002. N. Mukhtar and co-workers isolated **1** from *Conyza Canadensis* in 2002.[20] A. Ohsaki *et al* isolated eryhtrodiol from the l*eaves of Maytenus ilicifolia*[21] in 2004. D. Smati *et al* isolated **1** from *Zygophyllum geslini*[22] 2004. T. Akihisa *and co-workers* isolated **1** from *Chrysanthemum morifolium*[23] in 2005. F. Ullah and co-workers isolated **1** from *Rhododendron collettianum* in 2007.[24] M. Ahmad et. Al isolated **1** from *Datisca cannabina* linn in 2008.[25] M. E. Juan isolated **1** from various kinds of olive, *Olea europaea*[26] in 2008. A. Kumar *et. al* isolated **1** from the *stem bark of Erythrina indica*[27] in 2010. H. L. Chen *et al* isolated **1** from the stem of *Celastrus kusanoi* [28] in 2010. A. Aberham *et. al* isolated **1** from *Centaurium erythraea*[29] in 2011. J. P. C. Oliveira and co-werkers isolated **1** from *Lecythis pisonis* [30] in 2012. F. A. Hashem *et al* isolated **1** from *Mayodendron igneum*[31] in 2012. B. B. Cwynar *et.al* isolated **1** from *Tripterygium wilfordii* (thunder of god vine)[32] in 2014. M. M. Rashid *et. al* isolated **1** from *Manilkara zapota*[33] in 2014. G. M.Corres *et.* al isolated 1 from the aerial part of *Justicia acumina* (acanthaceae) in 2014[34]. H. S. Abbass *et. al* isolated **1** from the the leaves of *Ficus mysorensis* [35] in 2015. V. Soundararajan and co-workers isolated **1** from *Pterocarpus santalinus*[36] (red-sandalwood) in

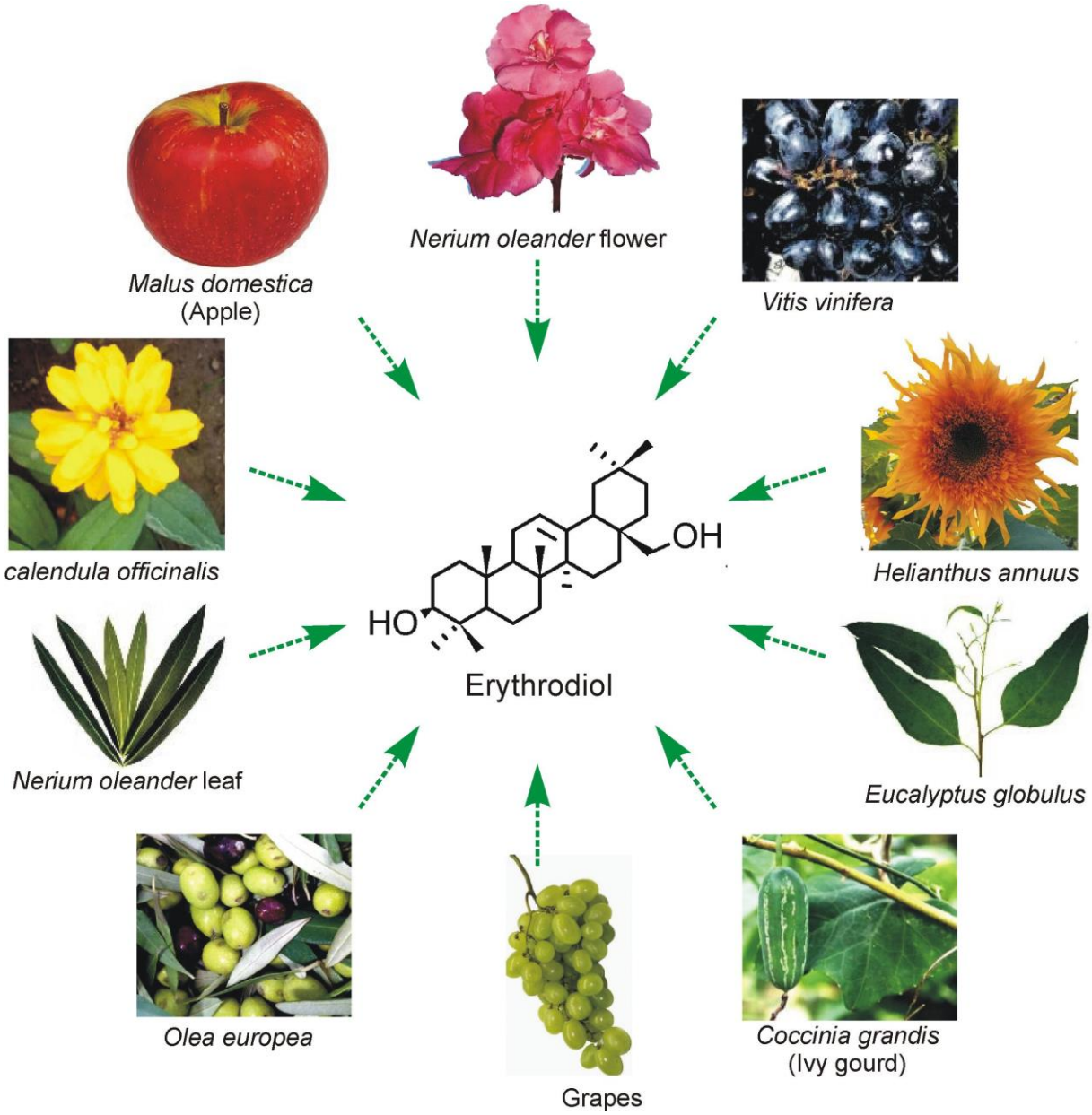


Figure 1: Schematic presentation of various natural sources of erythrodiol

2016. F. Ahmed *et al* isolated **1** from the leaves of *Callistemon citrinus*[37] in 2016. F. Pensec *et al* isolated **1** from *Vitis vinifera*[38] (grape vine) in 2016. N. Jan and co-workers isolated **1** from a flowering plant *Calendula officinalis*[39] (marigold) in 2017. W. Osman *et al* isolated **1** from *Tarconanthus camphorantus*[40] in 2019. (Figure 1)

3. Biological activity of erythrodiol

Erythrodiol ($C_{30}H_{50}O_2$), a naturally occurring plant secondary metabolite has been shown to have many medicinal activities like anticancer, anti-tumor, anti-inflamatory, cardioprotective, hepatoprotective, gastroprotective, antiproliferative anti-microbal, wound healing, etc. Moreover, computational studies have also been carried out depicting the biological activities of erythrodiol. (Figure 2-5)

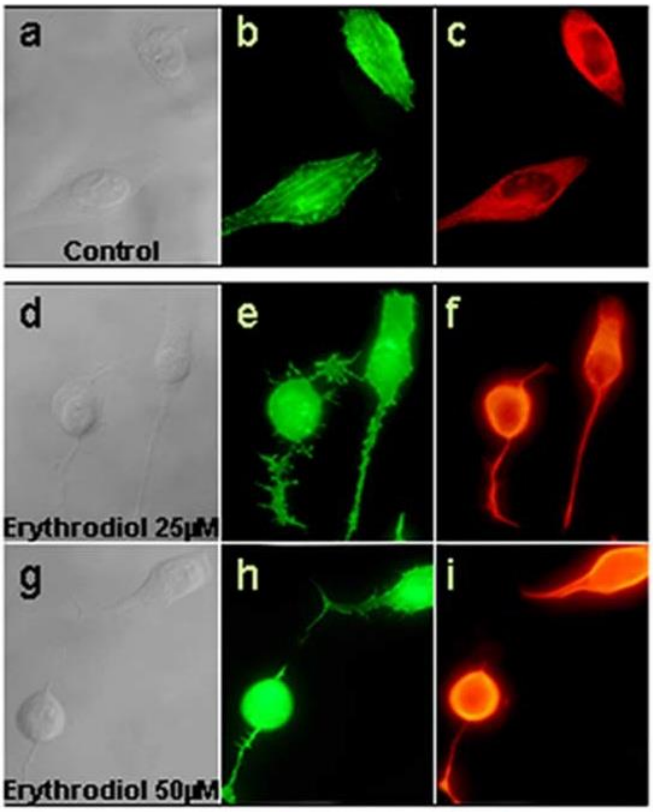


Figure 2: Erythrodiol induce morphological changes in the cytoskeleton. Cells were treated with different doses of erythrodiol for 6 h. Then, cells were stained with FITC-phalloidin (green, b, e, h,) or anti-vimentin Ab (red, c, f, i) and visualized under a fluorescent microscope (660). Cells were seeded on standard conditions. Adapeted with permission from Reference 36

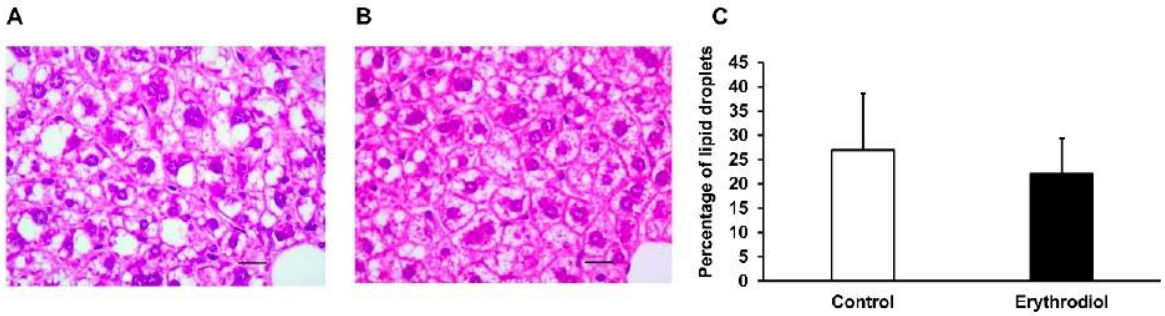


Figure 3: Hepatic histological analyses in male Apoe-deficient mice fed the different diets. Representative liver micrographs at 400X magnification from consuming a Western diet (A) and consuming a 10 mg/kg erythrodiol-containing Western diet (B). Liver sections (4 μm) from each mouse were stained with hematoxylin and eosin and blind evaluated. Bars denote 20 μm. Morphometric changes of hepatic fat surface in mice consuming the different diets (C) where data are means ±SD for each group (n= 14 and n = 15, respectively for control and erythrodiol). Statistical analyses were done according to Mann–Whitney's U-test. Adapted with permission from *Int. J. Mol. Sci.*, **2020**, 21, 7331, doi:10.3390/ijms21197331

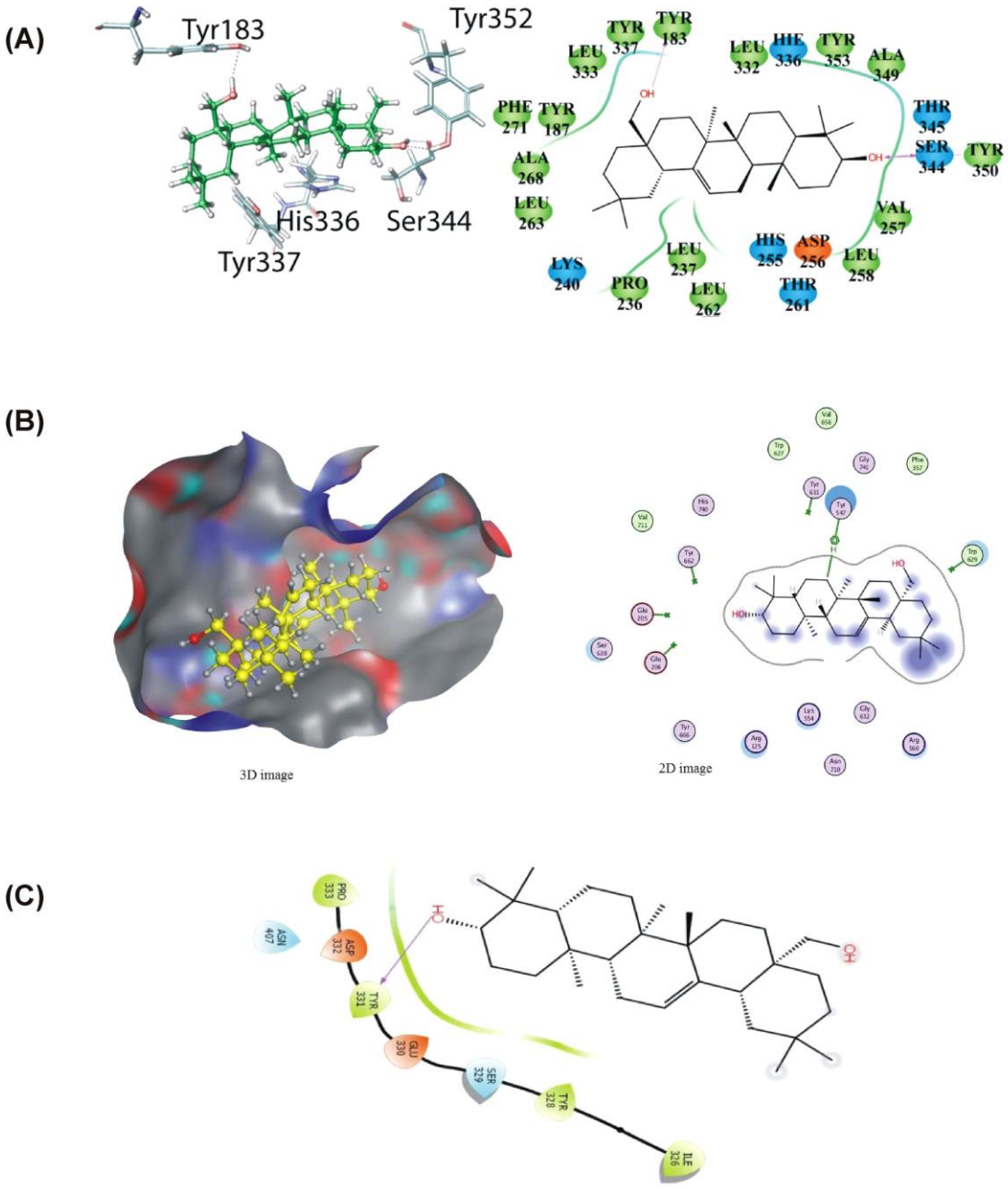


Figure 4. (A) Predicted binding poses with best induced fit score of erythrodiol using docking studies, adapted with permission (*J. Agric. Food Chem*., 2016, 64, 4511 − 4521) (B) Docking studies showing diagram interaction of Erythrodiol with DPP-4 enzyme related to anti-diabetic properties, adapted with permission (*Journal of Pharmaceutical Research International,* 2017, 19(4), 1-12), (C) Docking results of erythrodiol for breast cancer activity, adapted with permission (2019 – 4th International Conference on Research in Life-Sciences & Healthcare (ICRLSH) .

3.1 Anticancer and anti-tumor activity

Erythrodiol has been shown as a potent anti-cancer and anti-tumor active molecule in many biological studies.[34,42,43,44,45,46,47] H. Nishino and co-workers, in 1988 demonstrated that it has an inhibitory action against tumor promoter and shows remarkable suppressive effects on skin tumor formation in mice.[41] Erythrodiol also has been shown to have apoptotic and anti-proliferative activity towards human 1321N1 astrocytoma cell line and human MCF-7 breast cancer cell lines as demonstrated by M. E. Juan *et. al* in the 2008[42] and also by Y. Allouche *et. al* in the year 2011.[43] G. Yang *et. al* has shown erythrodiol posses high cytotoxicity against human SMMC-7721 hepatocarcinoma cell lines and human HO-8910 ovarian carcinoma cells in 2009.[44] S. R. Gedara and co-werkers has reported that erythrodiol has antioxidant and cytotoxic activities against HEPG2 liver cancer cell lines[45] in 2014. R. Martı´ *et. al* has shown that erythrodiol effectively affectes cell proliferation, cell cycle phases, induce astrocytoma cell death and a significant anticarcinogenic activity for the prevention and treatment of brain tumors and cancers.[46]**Error! Bookmark not defined.** (Figure 2) R. Abuobeid *et. al* in 2020 has shown that erythrodiol acts as a transcriptional modulator of hepatic gene expressions and a potential candidate to supress hepatocarcinoma into liver.[47] (Figure 3) O. B. Kazakova *et. al* in 2018, demonstrated that erythrodiol also posses apoptotic and anti-proliferative activity towards HT-29 human colon adenocarcinoma cells.[48] E. F. Khusnutdinova *et. al* showed that the derivatives of erythrodiol has a potent anti-tumor activity against various types of lung cancer (HOP-62, NCI-H23, NCI-H460 etc.), colon cancer (COLO 205, HCT-15, HT29, SW-620 etc.), breast cancer (MCF7, BT-549, MDA-MB-468 etc.), ovarian cancer (OVCAR-3 , SK-OV-3, etc.) and prostate cancer cell lines in 2018.[49]

3.2 Anti- inflamatory activity

Inflammation is a critical symptom in many chronic diseases like arthritis, tumours, diabetes, obesity, and metabolic syndromes etc. Damages caused by inflammation could be prevented with appropriate intake of dietary food supplements that possess anti-inflammatory activity. P. Shen *et. al* has demonstrated biotransformation of erythrodiol to have a significant nitric oxide (NO) inhibitory effect leading to the development of anti-inflammatory activity in 2020.[50]

3.3 Cardioprotective and vasorelaxant activity

There are many biological studies carried out by the scientific groups depicting the vasorelaxant and cardioprotective activities of erythrodiol.[51,52,53,54] The ability of erythrodiol to protect the cardio-vascular system from cardiac hypertrophy has been demonstrated by R. Martı´n and co-workers in 2012.[55] Moreover, erythrodiol has the ability to increase the cholesterol efflux level and contribute to the cardiovascular benefits. Moreover, during arterial thrombosis erythrodiol has been shown to inhibit platelet aggregation in a dose-dependent manner and thereby prevents cardiovascular injury as demonstrated by V. G. Kontogianni *et. al* in 2016.[56]

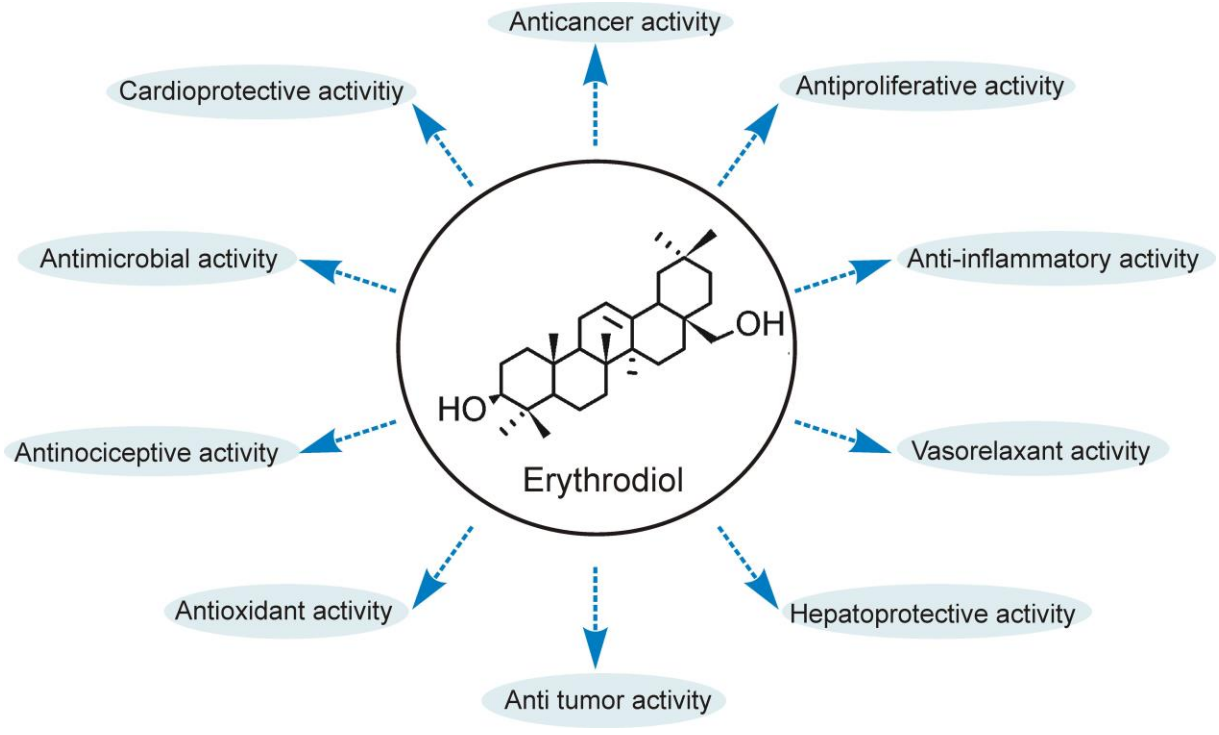


Figure 5: Schematic presentation of biological activities of erythrodiol

3.4 Anti-proliferative and apoptotic activity

There are many biological studies on the anti carcinogenic activities of erythrodiol but its cell biological functions in minute details are very rare. Biological studies carried out by M. E. Juan *et. al* on human colorectal carcinoma HT-29 cell lines, shows that erythrodiol has the effect on cell growth and apoptosis. The biological studies carried out with colon adenocarcinoma cells clearly depicts that erythrodiol exerts anti-proliferative and pro-apoptotic activity as demonstrated by M. E. Juan *et. al* in 2008.[57] Erythrodiol have also been shown to have anti-nociceptive effect as demonstrated by K. Kinoshita *et. al* in 1998.[58]

4. Conclusion and Future Prospects

In this review we have reported various natural sources of the oleanane-type dihydroxy pentacyclic triterpenoid erythrodiol ($C_{30}H_{50}O_2$). Moreover, various pharamacological and biological activities of the triterpenoid erythrodiol have been described. The nano-sized triterpenoid, erythrodiol having two hydroxyl groups (-OH) attached at the two opposite ends of the lipophilic triterpenoid moiety making it very useful for studying its self-assembly property for diversified applications in advanced materials, nano-biotechnology, etc.

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