Research Article

# Anthocyanins: Ethnomedicine to Clinical Trials

Komal Pandey[1] , Ashutosh Goswami[1], Khemraj Bairwa[1], Abhijeet S. Kate[1],Debanjan Chatterjee[2]*

**ABSTRACT:** Anthocyanins are the secondary metabolites chiefly present in the plant cell sap and vacuole. These are mainly responsible for attractive colors in leaves, flowers, and fruits. In the human being, anthocyanins are well known for their beneficial therapeutic effects such as prevention of cancer, oxidative stress, diabetes, obesity, etc. Owing to their huge therapeutic potentials, anthocyanins are highly consumed as a nutraceuticals form, herbal medicine, and functional foods. Chemically anthocyanins are flavylium cation linked with phenolic hydroxyl, methoxyl, and sugars groups. Therefore they are also known as polyphenolics with highly aqueous solubility. The sugar-free part of anthocyanins is known as anthocyanidin. Based on the position and number of hydroxyl and methyl groups, anthocyanins were classified in several types. Till now, more than five hundred anthocyanins have been explored which are classified in nine groups and fifty-nine subgroups. The pelargonidin, cyanidin, delphinidin, petunidin, peonidin, and malvidin are the commonly occurring anthocyanins in nature. Anthocyanins have a hydrolysable group and reactive scaffold which can easily act with the target protein and give plausible interaction. It also has the reactive oxygen species scavenging activity and hence acts as a potent antioxidant effect. Furthermore, anthocyanins are much explored as anti-obesity, antioxidant, anti-diabetic, and anti-cancer agents. Some anthocyanins are in phase 1 and phase 2 clinical trials for diabetes and obesity treatment. There are several world patents, united states patent, Chinese patents, and Korean patents on anthocyanins; particularly in the anti-diabetic area. Overall, the anthocyanins have been highly explored and are the high interest of molecules, but, there is no comprehensive review available for the scientific community which provides detailed phytochemistry, spectroscopic analysis, biosynthesis, biological activities, clinical status and patent-related information of anthocyanin. Therefore, in the present review, the authors tried to fill this gap by summarizing all the scientific information and researches on anthocyanins.

**Keywords:** Anthocyanins, Polyphones, Anticancer activity, Antioxidant activity, clinical status.

## INTRODUCTION

Healing, through nutritional therapy, is a pretty vintage concept. Since the inception of human civilization is being carried forwarded and continuously going on, this can give us peace not only our physique but also the soul and spirit (1). In the previous century, natural therapies include too functional foods along with medicinal food (2). The pharmacological effects of plants are mainly associated with secondary metabolites (3).

Anthocyanins are the complex polyphenolic and water-soluble plant pigments, and responsible for attractive pigments mainly in flowers, leaves, and sometime in stem and fruits. Anthocyanin comes from the Greek word "anthos" equals to "Flower" and kyaneos equals to "dark blue" in 1835 (4). Blueberry, raspberry, black rice, and black soybean having red blue-black colors are the few of the richest source of anthocyanin. The anthocyanins are generally synthesized in higher plants by phenylpropanoid pathway. European Union (5).

### Historical of anthocyanin:

In 1664 Boyle in his research color change has been noticed in "syrup of violet" intensified from purple to green which due to "acid liquor"; and the published first book on anthocyanins was "The anthocyanin pigments of plants" by Muriel Wheldale in 1916. Simultaneously, few more scientists were working on anthocyanins including Willstatter and Everest(1913), Willstatter and Nolan(1915), and Shibata. (1919) and concluded the depending upon the pH changes of anthocyanin colors of Centaurea cyanus flowers. They also mentioned the first time that the development of C. cyanus petal color is due to the conjugation of anthocyanins with metal ions (6). The molecular structure of anthocyanins was discovered by Richard Willstatter and co-workers from 1912 to 1916 (7). After this, Pauling 1939 proved the relationship between colour and anthocyanin. He suggested that colors in anthocyanins are due to the resonating structure of the flavylium cation. The colours of anthocyanins sometimes depend on the pH and pKa of the fluids cell sap and also responsible for particular pharmacological effect in human being (8).for instance, French people have a less coronary arterial disease as they used to take red wine enriched with anthocyanin (9).

Anthocyanins are well recognized in the traditional system of medicine including traditional Chinese medicine and Ayurveda. In France, anthocyanin formulations are widely used in motion sickness. In Germany, these are used in peristalsis and for reducing the gastric distress. Additionally, the recent biological studies also suggest the importance of anthocyanin as antiemetic, positive ionotropic, and as a potent morning sickness reducer in pregnant women. Chemically, the anthocyanins are flavylium cation linked with phenolic hydroxyl, methoxyl, and sugars groups. The aglycone of anthocyanins is known as anthocyanidin and glucose, arabinose, galactose, and rutinose are the most commonly found glycone in anthocyanins. Based on the number and position of hydroxyl and methyl groups, anthocyanins were mainly sub-classified into seven categories viz Aurantidin, Malvidin, Pelargonidin, Europinidin, Cyanidin, Petunidin, and Rosinidin.

This variety of anthocyanins has several biological effects over various organs or tissues including pancreas, liver, white adipose tissue, skeletal muscle. They may exert their various physiological effects via decreasing the glucose level, reducing the apoptosis, increasing the β cell viability, increasing the glucose uptake by skeletal muscle, and by reducing the insulin resistance. The safety and efficacy of anthocyanins were also evaluated in clinical trials by National Clinical Trials authority especially for anti-obesity, antioxidant and anti-cancer activities with NCL number NCT01245270, NCT01005420, and NCT 01883401 respectively. Additionally, plenty of patents including world patent or country-specific patents have been filed or granted on anthocyanin. Overall, the anthocyanins have been highly explored as potential therapeutic agents especially for diabetes treatment, inflammation, cancer, and an antioxidant. However, there is still a very less comprehensive review available on anthocyanins which describe the detailed phytochemistry, spectroscopic analysis, biosynthesis, therapeutic activities, clinical status, and patent. After conceiving these facts, the authors tried to fill this gap in the present review.

### Chemistry of anthocyanin

Anthocyanidins are the fundamental structures that are aglycones with anthocyanin and it consists of aromatic ring attached heteroaromatic ones, that is with oxygen bonded with C-

[1]*Department of Natural Products, National Institute of Pharmaceutical Education and Research- Ahmedabad, Palaj, Gandhinagar-382355, Gujarat, India.*
[2]*Department of Natural Products, National Institute of Pharmaceutical Education and Research- S.A.S Nagar, 160062, Punjab, India.*

*Correspondence: Debanjan Chatterjee, Ph.D. Research Scholar, Department of Natural Products, National Institute of Pharmaceutical Education and Research- S.A.S Nagar, 160062, Punjab, India.Tel: +91- 7980568998, E-mail: debu06781@gmail.com*

C in the 3rd aromatic ring (10). Pauling 1939 shows the color and proved the resonating effect and structure all around literature reported more than five hundred anthocyanins and among them, only 58 subclasses and then that have more or less 23 anthocyanidins with the 6 different have vascular plants (11). These most commons are Pg, Cy, Pn, Dp, Pt, Mv. There are nonmethylated anthocyanidins that is Cy, Dp, Pg maximum in nature. (12) Among the above 82% are pigmented fruits and some of vegetable. Then 69% of fruits almost 49% in flower distribution more than 61%, in Cy 51% Dp 12% Pn 12% Pg 12% Pt % Mv %. The widely spread things 3 monoxides, 3 biocides 3, 5- 3, 7 –glucoside. They are most present in Cy -3- glycoside. Enormous groups present for the natures beauty. the chemotaxonomic and the adulteration variety also found due to their componential analysis and related compound percentage (13) (14).

2 Phenyl benzopyrilium and flavylium salt main derivatives of this hydrolyzable, they are poly hydroxyl poly methoxy of the anthocyanin moiety. The hydrolyzable groups are methylating in nature and they are attached with sugar molecules. Hundreds of molecules are the same category and they have the carbon skeleton (15). Characterization is done based on the spectrophotometric and the spectrometric tools. Natural resources have a large variety over three chiral centres and their varieties this is also has the same. The hydroxyl groups present and the related derivatives there hemiketal and hemiacetal groups also shown a good number of activity in vivo and in vitro (16). If we found the derivatives they are the hydroxyl methoxyl methyl, methoxy ether. Biosynthetic pathways are the same for the ethoxy mether group anthocyanins. The flavonoid class has the main identity of the 3 ring skeleton and so on anthocyanin likewise (17).On a general time, sugar is attached with C-3 and C-5, exceptional case C-7, then glucose arabinose and galactose are also attached to this. Most frequently acetylation gives the sinapic acid, ferulic acid, acidic acid, and para coumaric acid. Acetic acid , malonic, oxalic and malonic acid. Anthocyanins have a natural shielding of aqueous attack. Bathochromic, hypsochromic shifts are also there in UV spectra. According to the variability structure the anthocyanin has fragmentation variety and there isomerization pattern on each and every spectra (18).

**Ground state chemistry of anthocyanin**

Anthocyanin at acidic pH <2. 5 have good ground-state chemistry and they give the study of anthocyanin in aqueous solution and when it is in the hydrolysable fluid then only it gives the ground state. It usually forms the AH+ flavylium cation that is pH 3, they occur the nucleophilic attack then the loss of proton give the yellow color with the hemiacetal and hemiketal form B (19). Ring-opening tautomerism can occur for ring B it forms hydroxy chalcone and Z-hydroxychalcone. Which will be isolyzable thermolizable and and it is formally the state when multiple equilibrium is needed (9). Conjugate pH which raises quickly form conjugate base. Then with water, the A can observe the pH initially nucleophilic attack at 7 pH. Additional colours for the additional deprotons and losses the main colour and hence stabilized by the effective loss of pigment stabilization. This requires because of the food colour and pigment as they are much reliable on the food customer based product (20).

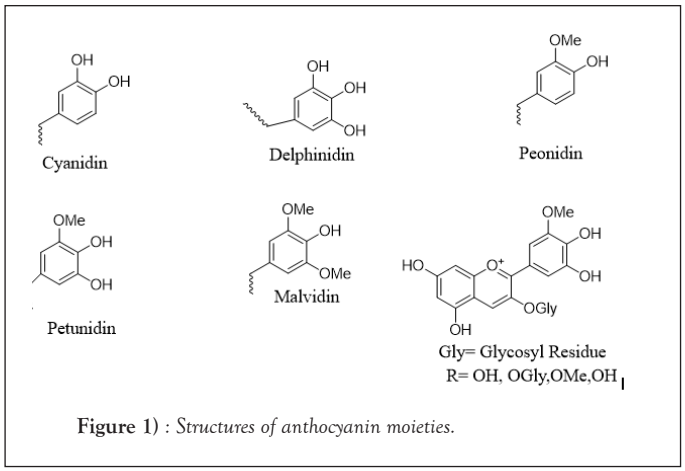
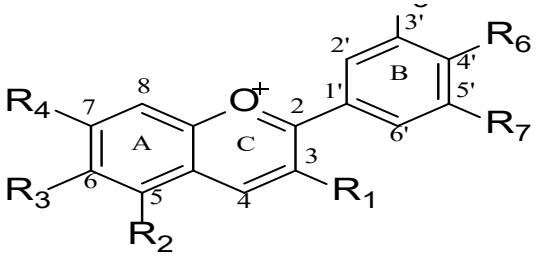



**Figure 1)** : *Structures of anthocyanin moieties.*

**Classification of anthocyanin**



Anthocyanin its glycoside and anthocyanin chemical structure is shown here

3 glucosides of the anthocyanidins are the main functional sugar group. Anthocyanidin is bifurcated sometimes sugar free anthocyanins aglycones and glycones. Literature data shows as of now 58 are reported in literature later the amount is increased more or less five hundred different anthocyanins example wise but the chemical structure is 59 moiety based they have different derivatives but the core scaffold is same shown over here. this are all literature data (14) (21) (22) (20).

**Structural moieties of anthocyanin class are given below-**

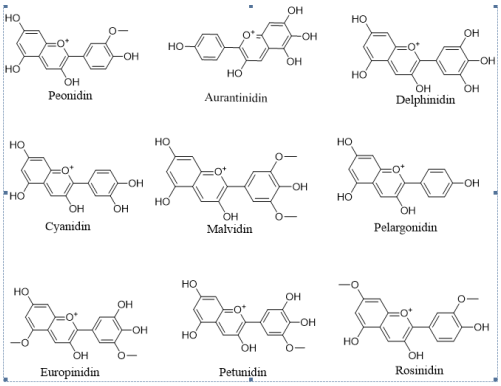
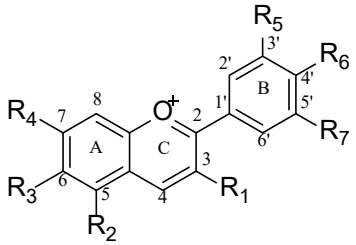



Figure 2 Subclass of anthocyanins.

**Common anthocyanin and anthocyanidin derivatives**



**Biological activity**

Attractive colour is one of the most salient features of anthocyanin, like red, blue. When they are in plants the attractiveness shows cross pollination and protect and harmful effect of UV (24). Some colorant company they used to manufacture colour by these natures anthocyanin. they have a highest use in horticulture (25). Sometimes in the structure variety they show that B ring substitution glycosylation acylation with the cinnamic acid for the pigment stability. Anthocyanin pigments are very much effective and they have much effect in the radical scavenging activity for humans. Anthocyanins used as an anti oxidant and these have considerable health benefit anthocyanin based drugs nutrient are in clinical trials and they are also considered by different regulatory agencies of different companies (26).

**Bioactivity of anthocyanin pigments**

Intensified data of anthocyanins as a pigment shows that this can reduce the risk of coronary arterial disease, stroke, anti carcinogenic effect, anti Inflammatory, beneficial for improving visual acuity level and last but not the least cognitive function (27). Literature says this has a good anedoctal accounts this are also having good folklore action for the ethnic people and as a tribal medicine. For improved night vision and visual acuity the RAF force of british army they are treated with bilberries (28), Chernobyl victims feeded by Aronia melanocarpa(chokeberry) products to ameliorate effects of gamma radiation exposure. Components of red wine is highly accepted for the polyphnolic groups and due to that the antioxidant activity (5). The anthocyanin pigments are good scaveing activity and have a free radical scavenging activity towards the ROS , which have been demonstrated in vitro through such assays as oxygen radical absorbing capacity(ORAC). Various literatures show that cyanidin have much more activity than malvidin and malvidin have some less activity that pelargonidin. The effect of glycosidic substitution and acylation on the Oxygen radical absorbing capacity which is resulted in a marked increase in ORAC assay. Glycosidic substitution influenced ORAC activity, but not in a predictable manner (7). in vivo study with animals and there behavioural test are convincing. Various reviews shows that red cabbage they reduce the tumour of a rat, that are also have been due to the effect of anthocyanin (29).

This effect that is improved by dietary supplement with blueberry and strawberry extracts. In Italy, they develop one clinical study on that study they(160 mg twice daily for 1 month) exhibited improvement of diabetic retinopathy and nephropathy at the end of the trial (30).Intact content of anthocyanin glycoside found in human urine (32).

**Different biological activity of Anthocyanin**

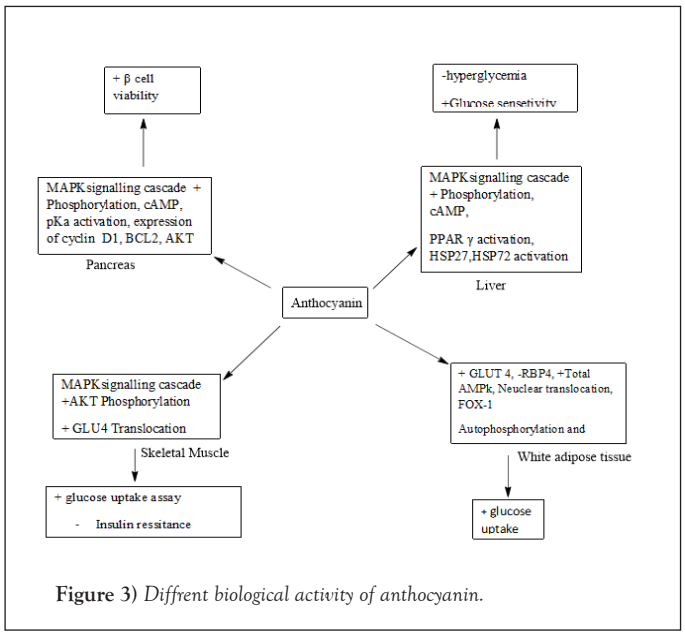



**Figure 3)** *Diffrent biological activity of anthocyanin.*

**Biosynthetic pathway**

**Biosynthetic pathway overview**

Like other biochemical pathway anthocyanin pathway has a responsibility to produce anthocyanin pigments, the plants which give anthocyanin pigments tissue. This pathway consists a group of genes and the enzymes that are very much relevant (39). total 6 genes are core they diversified taxonomically and some other are clones by genetic mutation. The plant species Maize and snapdragon have the 2 different type of genes, literature shows that they have also cloned the 3rd one, the common morning glory, Ipomoea purpurea (40). The additional information provides the gene sequencing among the single genetic pathway (41). The genes shows different evolutionary pathway. The adaptive gene takes the pathway some other way. Regulatory gene associated with the anthocyanin pathway the adaptive gene is for the flower colour and the pigments. Sometimes structural genes also have some capability to show function in increase vacuolar fluid and details. For the individual anthocyanin genes these 3 genes heterogenecity is seen in major angiosperms. Many times CHS type gene are in indicating without co ordinate the adjusting pathway (42) (43).

**Figure mentioned** anthocyanin biosynthetic pathway in angiosperms, the enzymes are CHS - chalcone synthetase CHI – Chalcone flavones isomerise, F3H flavanone isomrase, F3H flavones hydroxylase, DFR - Dihydroflavonol reductase, ANS- Anthocyanidin synthetase, and UDP3GT – UDP glucose flavonoid 3 oxy glucosyltransferase (44)

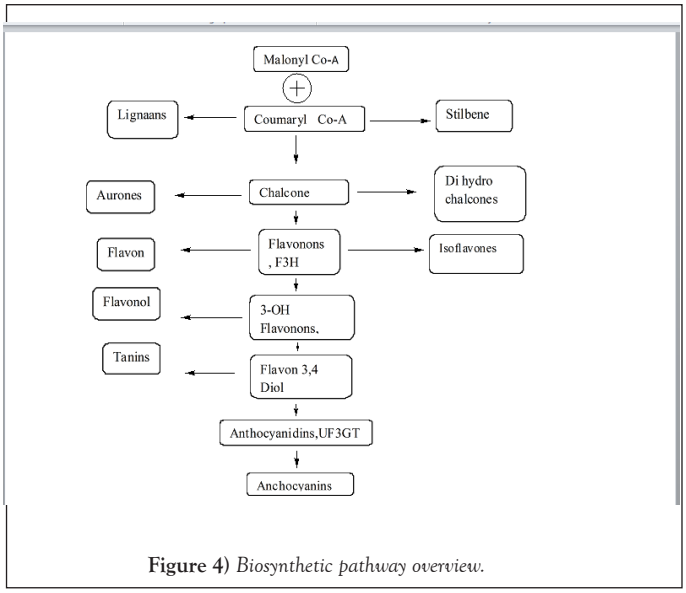



**Figure 4)** *Biosynthetic pathway overview.*

**The biosynthetic mechanism of anthocyanin pathway –**

Biosynthetic pathway of anthocyanin the well established as a network of many pathways. This pathway correlates with the flavonoid pathway also starts with chalcone synthtase synthesized naringenin chalcone from four coumaryl CoA and malonyl – CoA. After that chalcone is being isomerized by naringenin. It isomerise CHI from naringenin. Naringenin is converted by the flavonoid 3-'hydroxylase or flavonoid 3, 5 hydroxylase into 2 other biflavonoids, that is dihydroquercitin and dihydromyrecetin. Respectively the next 3 pathway are same fashion. By DFR Dihydroquercetin followed by leucocyanidin by ANS then cyanindin then by biosynthetic process they have done the leucodelphinidin (45). Cyanidin pelargonidin delphinidin converts to anthocyanidin and cyaniding 3 glucosidase pelargonidin 3 glucosidase and delphinidin 3 glucosides form the anthocyanin (46). The 2 enzyme F3H and F'3'5H are diversified and determined by the B ring hydroxylation and sometimes DFR also responsible for the composition and pigmentation. This diversification varies through genus species based, altogether they all having the same biosynthetic pathway with some enzymes and all same process fields and mechanism is alters (47). But the individual steps mechanisms of action were different as oxidation reduction occurred and the coloured interaction of each level has been changed (41).

**Chemistry of anthocyanin degradation**

pH solution have a capacity to show colour in different pH. Red colour will show in pH 1 the flavylium cation. Sometimes they show blue and red colour also due to the variation of pH and the change in metal ion and the complexations. pH 2, 4 for purple and red. the quinoidal colour that is the blue predominath when ph 5 to 6, that is the carbinol pseudobase and a chalcone (3). pH value sometime 7 when the anthocyanins groups are degraded. Then the pH value is changed mainly structural pH are 4 to 6 normally seen in yellow chalcone. Flavylium is helped out when it is cation of or pH is increased. like the litmus theory it always shows the normal colouration The groups that are in ring A and B are much more effective in changing of this colour that is why when derivatization occurs it shows the same theory (55). Pelargonidin that is the most stable based on there aglycone property and monoglycosides and diglycosides are available as a

stable anthocyanin. In degradation reaction they follow the colour change basis of phenolic and aldehyde compound mainly basis of degradation reaction. The stability of anthocyanin is also the pH specific (35, 58).

**Anthocyanin in clinical trials**

Anthocyanin has different phase of action against different field of disease among them diabetes is one of them, another antioxidant, anti obesity, there are different derivatives of anthocyanin are associated among them some are good clinical agent too (60). Molecules that are under clinical trials are different type of majorly anthocyanin molecules in the field of anti obesity and anti diabetic they are in clinical trials they show the pathway in different pathway. Majorly the standardized drug are reported for the AMPK phosphorylation and the GLUT-4, CRP-1, PPAR-‖ IRS-1 pathway (61). They follow sometimes AKT pathway some are WNT. Sometimes used through gene expression RBP-4 and SREBP expression. mRNA based expression system is also there for inhibiting the fatty acid and the trigycerol synthesis enzyme. The downregulation always by the lipogenic factors (62).

Anthocyanin stability is depend on different buffer solutions and during storage. Different storage condition and pH 1.0,4.5 is showed still attractive colour in red and violet. Depending upon of the colour of anthocyanin , anthocyanin degradation and its storage is first order kinetics. The reaction rate(r) expressed first order and the conc based on single reactant (A) which raised to first power (72).

r = d[A]/dt= k[A]

k is the first oder kinetics unit is S-1

Arranging the equations

d[A]/dt= -kdt

pH and the stability study with heat is useful for the study of degradation chemisty and other anthocyanin. Anthocyanin and anthocyanidins as a natural dye , these coloured pigment and potential colour are most stable of anthocyanin class , because they have a solubility issue.Anthocyanin have several sub class and they are potential colouring substance , yield wise in fruit also they have 50%,12%,12%,7%,7% of cyaniding, delphindin, pelargonidin, peonidin, malvidin and petunidin , respectively. Their stability basically depend upon the ph and their light stability copigments, pigments , temperature , pH metal ions , oxygens , antioxidants. The B ring of anthocyanin moiety is mainly responsible for the stability in solution. That is why the colour changes in solution depend the anthocyanin stability. and successively the colour is depend upon the pH. Polymerization of anthocyanins due to tannins is also used to increase colour stability at lower pH. These colouring agents are much more appreciable in case of their food additives USFDA also approved anthocyanin as a colouring agents (73).

**Root cause analysis**

Anthocyanin, natures pigment they are the normal phytoconstituent. It has a large use in the field of pigment industry , colour industry. To make food lucrative, lustrus ,glossy,colouring agents are sometimes used for these purpose. But for drug candidate for the best therapeutic activity it is not still been explored,some potential candidate have been through the drug discovery phases but fall down.The root cause of this is their stability,as we know the anthocyanin has the sub class of flavonoid having 3 aromatic ring and the middle ring have one ion that is positive cation. It is sometimes the flavylium ion. If we see any anthocyanin product stability we can easily see that the quinoid base have some chemical reaction, specially the oxidation and the reduction in presence of air.Quinoid base is reduced and it form the flavylium ion. then it get hydrolysed by moisture and form the hemiketal compound.The hemiketal compound then moved to the chalcone formation and chalcone can not be a anthocyanin it is a flavonoid which is basically toxic.Furthur addition if we take this chalcone molecule also it can also further sub divided and form the phloroglucinol aldehyde and the protocatechuic acid, means the chalcone moiety is getting reduced and form the aldehyde and carboxylic acid (74).

Here the scheme of the degradation of the hemiketal form to the flavylium ion

Beneath that we have shown the formation of aldehyde and carboxylic acid formation. So as we can seen the anthocyanin molecule has a large chance to getting reduced. So if we used it as a potential candidate and the basic structure then it may degrade the final product. In the pharmaceutical formulation study there are some class of drug they are high permeability but low solubility largely known as BCS class 2.The anthocyanin formulations are BCS class 2 drugs and that is why. This class of drugs can not be all time diluted or soluble they have some issue of solubility also. That is why by overcoming all this obstacles it is very hard to develop anthocyanin as a potential drug candidate. But technology develops , a large class of drugs are now administered through nano formulation and nano crystals. it can help in stability and there is a possibility of potential drug candidate (75).

An acylated cyanidingly cosidein the red - purple of xlaeliocattleya cvminipurple

**Future perspectives**

Metabolic property all time not supplied by our body some times it is needed based on the physiological condition , sometimes they are isomers and they have same metabolic property.The anthocyanin and anthocyanidin drug development story is such kind of chemical instability problem which are against of some natural properties.It has also some biphasic conditions for acceptable period and it also helps for chemoprevention anti carcinogenic robust , and also helps modify of studies.These are the sort of anti obesity drugs also a clinical candidate of anthocyanins, is clearly superior parts of anti obesity drugs. Presently pre clinical and clinical differences and the questions conclusively if th mixtures developed the appropriate strategy have show anthocianin as a good pharmacokinetic agent.Though some stability problem arises in many case of compounds don't have proper stability and the mixture contains some degradants. Presently the anthocyanin products that are in market are well established , researchers are doing study for there components profile of individual mixture of components. Study also shown that the mixture can also the thing which contains fruits and many components may contribute to the chemopreventive efficacy.

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