

THE MIRACLE OF RETINOL

Why is there still so much fuss about retinoids and retinoid-like products? asks Ratan Chaudhuri

What are retinoids?

Simplistically, retinoids have been defined as vitamin A (retinol) and its derivatives, such as vitamin A aldehyde (retinal), vitamin A acid (retinoic acid, all trans retinoic acid, atRA), comprising the so-called natural retinoids. Retinoic acid is considered to be the active form of vitamin A and is involved in gene regulation, leading to differentiation and apoptosis of normal and cancer cells. The conversion of retinol to retinal by the P450s is considered to be the rate-limiting step for the biosynthesis of atRA.

In addition to retinol dehydrogenases, P450s 1A1, 1A2, 1B1, and 3A4 have recently been shown to be the major human P450s that catalyse this reaction. Subsequent research has resulted in a much larger class of chemical compounds that are termed retinoids due to their biological similarity to vitamin A and its derivatives. Retinol is found in a variety of foods. It is mostly found in beef, veal, chicken liver, eggs and fish. Retinol is also present in vegetables such as carrots, squash, sweet potatoes, pumpkin and cantaloupe.

Why is there so much buzz about retinol?

When we speak of retinol, we always associate it with beauty and anti-ageing products. Retinoic acid (retin A) became popular over 20 years ago as an anti-acne treatment. Doctors and patients soon discovered another benefit, one with enormous impact on those who were looking for a way to look younger.

Retinol has anti-ageing effects but is less aggressive to skin than retinoic acid. The anti-ageing effects of retinol are being enjoyed by people from all over the world. If you do a Google search for 'retinol products', you get 743,000 hits. If you go to dermstore.com, you'll probably get all the information you need for retinol-containing finished products. There are 49 pages to browse and then select one product from on dermstore.com; it's a tough job to select one from this list. You'll get products from almost all major brands. Johnson & Johnson company RoC was the first to formulate stabilised retinol and has become an expert in this anti-ageing ingredient.

With so many doctors and beauty companies on a search for the next big anti-ageing product, why do retin A and retinol still have so much appeal after its first use some 20 years ago? The answer is simple – they work, and its effect has been demonstrated on the molecular level. If you are interested in the true science behind retinol and retinoic acid, you can read articles from John Voorhees, dermatology department at the medical school of the University of Michigan.

With consistent and continual use, retinol is effective in fighting and reversing the signs of ageing. It is not as aggressive as retinoic acid and is therefore suitable for sensitive skin. And the results are not just cosmetic. Retinoic acid and its synthetic analogs are potent regulators of a diverse group of biological processes. On the other hand, pharmacological doses of RA and several synthetic analogs have been shown to be effective in the prevention and treatment of a number

of types of cancers and in the treatment of a variety of dermatological conditions.

Why isn't everyone using retinol products?

If it's so well studied and works so well, why isn't everyone using retinol? Well, nothing in this world is perfect. Needless to say, retinol is nowhere close to being a perfect product and it has many problems.

The first problem is instability. Retinol degrades very easily in the presence of air and sunlight so a jar, clear container or any container that exposes the product to air will render retinol worthless. It is also very difficult to formulate due to its instability. To be beneficial, retinol should be packaged in tubes, capsules or pumps that don't allow air in. Retinol products cannot be used during the day, again due to its photochemical instability.

The second problem is retinol's skin irritancy and skin sensitivity. Use of retinol can make your skin look red and irritated and increase skin sensitivity to sunlight, so be sure to use a sunscreen. People with rosacea (a condition that causes skin redness) are not recommended to use retinol products.

The third problem is retinol's overdosing. The following information is obtained from Wikipedia: Too much retinol can be harmful or fatal, resulting in what is known as hypervitaminosis A. Excess retinol during early pregnancy has also been associated with a significant increase in birth defects. These defects may be severe, even life threatening. Even twice the daily recommended amount can cause severe birth defects. The FDA currently recommends that pregnant women get their vitamin A from foods containing beta carotene and that they should ensure that they consume no more than 5,000 IU of preformed retinol (if any) per day. Although retinol is necessary for fetal development, most women carry enough in their fat cells, so over supplementation should be strictly avoided. Topical application of retinol or retinoic acid during child bearing age must be avoided.

Why is there so much buzz about retinol-like claims?

It's exciting to see all the research going into the area of anti-ageing, but even after 20 years of retinoid use they are still the product most recommended by dermatologists. That's because retinol addresses all three major skin care/treatment issues – reversing ageing, protecting skin from further damage and improving problem skin, such as acne. There is so much information available, it is almost impossible to go through each and every article written on retinol. Just look at the number of hits you get: 5,580,000 on



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Ratan Chaudhuri has over 20 years' experience working with C&T ingredients suppliers. US-based Sytheon was established in 2006 to conduct research and market active ingredients worldwide for skin care and dermatological use. It takes a natural approach to satisfy key value drivers – safety, effectiveness, stability and differentiation
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Retinol addresses all three major skin care issues – reversing ageing, protecting skin from further damage and improving problem skin



Retinol has amazing anti-ageing properties but also a whole host of problems

Can you imagine a product with all the major benefits of retinol but none of the problems? That really would be a dream material

Yahoo and 1,950,000 on Google. It is easy to understand why ingredient suppliers often claim new products as retinol-like, almost always taking very minor functional attributes of retinol.

Can you imagine a product with all the major benefits of retinol but none of the problems? That really would be a dream material.

How do we know whether we have a retinol-like product?

Before we claim a product is retinol-like, let's look at the criteria one should consider to make such a claim. Since retinol has a wide range of activity, gene expression profiling of retinol vs the retinol-like compound may be the right choice for making such a claim. In the field of molecular biology, gene expression profiling is the measurement of the activity (the expression) of thousands of genes at once, to create a global picture of cellular function. These profiles can, for example, show how the cells react to a particular treatment. DNA microarray technology measures the relative activity of target genes. There are other methods available but DNA microarray gene expression is far more common, accounting for 32,803 PubMed articles as of 7 February 2010. So it often makes sense to perform semi-quantitative DNA microarray analysis to identify candidate genes and then perform rtPCR (real time polymerase chain reaction) on some of the most interesting candidate genes to validate the microarray results. Data analysis of microarrays has become an area of intense research and is beyond the scope of this column. A group of genes up- or down-regulated by at least two-fold with a p-value of 0.05, an estimate of how often we would observe the data by chance alone, can be taken as a criteria to look for a functional analogy of a compound to retinol. Gene expression profile can thus be considered as a molecular signature of a compound.

How do you compare molecular signatures of retinol and retinol-like compounds?

A simple comparative microarray experiment needs to be carried out side by side with retinol and retinol-like compounds under identical conditions to define the molecular signature of the two compounds and then

including the results in volcano plots. A volcano plot is a type of scatter plot that is used to quickly identify meaningful changes in large datasets, such as data from DNA microarray analysis. It plots significance versus fold-change on the y and x axes respectively. It is constructed by plotting the negative log of the p-value on the y axis (usually base 10). This results in data points with low p-values (highly significant) appearing towards the top of the plot. For example, if a p-value of 0.05 is set as the threshold for statistical significance, all points situated above the value of 1.3 on the y axis are statistically significant. The x axis is the log of the fold change between the two conditions; if two-fold change is set as the threshold, all points to the right of 1 and to the left of -1 on the x axis are of interest.

In summary, plotting points in this way results in two regions of interest in the plot: those points that are found towards the top of the plot and that are far to either the left or the right hand side. These represent values that display large magnitude fold changes (hence being left or right of centre) as well as high statistical significance (hence being towards the top). Volcano plots of Sytenol A and retinol are shown here.

These plots clearly demonstrate dramatic similarities in gene expression profile between Sytenol A and retinol, hence this data confirms the functional analogy of Sytenol A to retinol. It seems Sytenol A is indeed a true retinol-like compound.

Structurally Sytenol A is phenol, 4-[1E, 3S)-3-ethenyl-3, 7-dimethyl-1, 5-octadienyl [INCI: Bakuchiol]. It is a highly purified Bakuchiol (purity >95%) that is obtained by extracting and purifying Babchi seeds from India using a proprietary process. It comes as a pale yellow viscous oil. Sytenol A has excellent photochemical and hydrolytic stability, a good safety profile and is easy to formulate due to its miscibility with a wide variety of emollients and solubilisers. Human Repeat Insult Patch Test (HRIPT) at 5% dilution in corn oil showed no skin irritation or skin sensitiaation. Taken together, DNA microarray, qtPCR results and cell culture studies (not discussed here) demonstrate the potential of a true retinol-like compound (highly purified Bakuchiol) that could become a key ingredient for dermatological or skin care and treatment applications.

