Biotransformation in the Oleochemical Industry

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Biotechnology has assumed a role in industry at the interface between biology, chemistry and engineering. Its existence can be traced back for over 150 years in the application of the technology for manufacturing industrial chemicals. History shows how manufacturers turned biological catalysis to their advantage in the past. The manufacture of ethanol by chemical synthesis which originated in the 19th century serve as an example. From the chemical route, manufacturers turned to fermentation processes for the manufacture of ethanol, and fermentation now accounts for over 90% of ethanol production in the United States.

During the last 25 years, significant developments in the field of organic chemistry have seen the application of biological systems to chemical reactions. Biological materials have been used for the preparation of pharmaceuticals, food additives, commodity chemicals and fine chemicals (Steele and Stower, 1991; Malcata *et al.*, 1990). Such technology is called microbial transformation or simply biotransformation and is a rapidly developing area of biotechnology combining microbiology, biochemistry, organic chemistry and engineering (Turner, 1995; Yamada and Shimizu, 1988).

BIOTRANSFORMATION

Biotransformation is defined as a process in which a biocatalyst is used to convert a raw material into a value-added product. The biochemical reaction can be performed by intact microbial cells or catalysed by enzymes. Some reactions are complex requiring several enzymatic steps and possibly also cofactors, while others have only a single step which can be accomplished by using isolated enzymes (Casey and Macrae, 1992). The range of reactions which can be catalysed by microbial enzymes includes nearly all chemical types (*Table 1*).

TABLE 1. REACTION TYPES MEDIATED BY MICROORGANISMS

Oxidation	Hydroxylation; epoxidation; dehydrogenation; oxidation of alcohols and aldehydes; oxidative degradation of alkyl chain; oxidative deamination; oxidation of hetero-functions; oxidative ring fission.
Reduction	Reduction of organic acids, aldehydes, ketones; hydrogenation of double bonds; reduction of hetero-functions; dehydroxylation;
Hydrolysis	Hydrolysis of esters, amines, amides, lactones, ethers and lactams. Hydration of double bonds and epoxides.
Condensation	Dehydration, *O*- and *N*-acylation, glycosidation, esterification, lactonisation and amination.
Isomerization	Migration of double bonds or oxygen functions, racemisation,

CHARACTERISTICS OF BIOTRANSFORMATIONS

Biochemical reactions performed by microorganisms or catalysed by enzymes are essentially identical to those carried out in conventional inorganic or organic chemistry. The enzymes operating in microbial transformations increase the reaction rate by lowering the activation energy as normal catalysts do. However, the most striking difference from non-biological chemistry is the substrate specificity. The catalytic activity is also usually restricted to a single reaction type so that side reactions are not expected as long as a single enzyme is involved. The substrate molecule is usually attacked at one specific site, even if several groups of similar reactivity are present. The reactive centre of an enzyme provides an asymmetrical environment which distinguishes between the enantiomers of a racemic substrate. Thus, only one of the enantiomers is attacked. The reactions generally occur under mild conditions unlike those obtained with chemical catalysts which rarely function at temperatures below 40°C, at a pH near neutrality and at atmospheric pressure (Leuenberger, 1984). Therefore, even labile molecules can be converted with low energy consumption without undesirable decomposition or isomerisation. Thus, biotransformation provides a means for unique reaction types.

PRODUCTION OF OLEOCHEMICALS

There is a considerable interest in utilizing natural resources such as vegetable oils as renewable feedstock in the preparation of useful chemicals, particularly oleochemicals (El-Sharkawy *et al.*, 1992). Similar products may be synthesised from petrochemicals (Richtler and Knaut, 1984). With respect to biotransformation, oleochemicals may have an edge over petrochemical feedstock because a wide range of enzymes acting upon compounds such as triglycerides, fatty acids or fatty alcohols occur naturally (Schmid, 1987).

Oleochemicals have many applications in the chemical industry (*Table 2*). The current technology for producing oleochemicals centres around the chemical modification of natural oils and fats from plants and animals (Baumann *et al.*, 1988). The use of chemical catalysts results in relatively low versatility, requires high temperature and usually achieves only low specificity, giving rise to racemic mixtures which require refining. Biotransformation is an approach that is beginning to be exploited for the production of oleochemicals (Casey and Macrae, 1992). It can provide the oleochemical industry with improved raw materials, high quality products, environmental friendly (biodegradable) products, and processes that consume less energy and generate less waste.

BIOTRANSFORMATION OF FATTY ACIDS

Industrial transformation of natural fatty acids has focused primarily on the transformation of carboxyl groups and reactions at double bonds or hydroxyl groups (Werdelmann and Schmid, 1982). Apart from the alpha-methylene group, the alkyl chain of saturated aliphatic fatty acids is not readily accessible to chemical derivatisation (Baumann *et al.*, 1988). More than 90% of oleochemical reactions occur at the fatty acid carboxyl groups, while less than 10% involve rearrangement of the carbon chain (Richtler and Knaut, 1984). However, biotechnological processes open up the possibility of specifically attacking even non-activated positions of the fatty acid chain. *Figure 1* shows the possible transformations of fatty acids.

CONVERSION OF SATURATED FATTY ACIDS

Stearic acid is one of the cheapest raw materials from fats and oils. It is used as a starting material for the production of cosmetics, lubricants and detergents, but little information is available on the biotransformation of stearic acid. A strain of

TABLE 2. AREAS OF APPLICATION OF OLEOCHEMICALS IN THE CHEMICAL INDUSTRY

Fatty acids and derivatives	Plastics; metal soaps; washing and cleaning agents; soaps; cosmetics; alkyd resins; dyestuffs; textiles; leather and paper products; rubbers; lubricants.
Methyl esters of fatty acids	Cosmetics; washing and cleaning agents.
Glycerol and derivatives	Cosmetics; toothpastes; pharmaceuticals; foodstuffs; lacquers; plastics; synthetic resins; explosives; cellulose processing.
Fatty alcohols and derivatives	Washing and cleaning agents; cosmetics; textiles; leather and paper products; mineral oil additives.
Fatty amines and derivatives	Fabric conditioners; mining; road-making; biocides; textile and fibre industries; mineral oil additives.

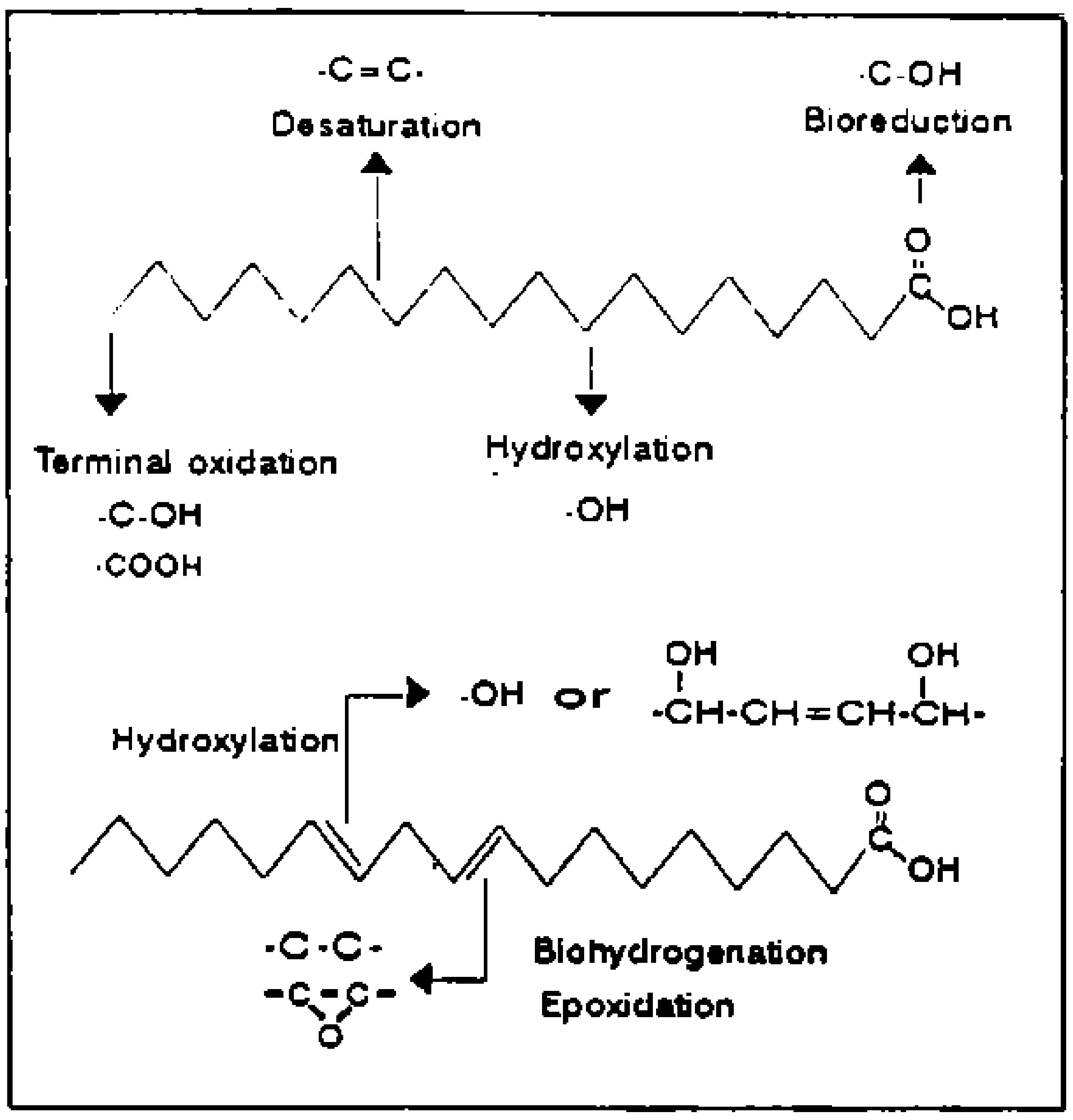

Figure 1. Possible reactions in the biochemical transformation of fatty acids.

Pseudomonas cepacia converted stearic acid to maleic anhydride derivatives (Esaki *et al.*, 1994b). A strain of *Candida rugosa* produced D-beta-hydroxy acids from short chain fatty acids. Other fungi are able to convert short and medium chain fatty acids, particularly those of C6 to C12 chain length. Biotransformation of mixtures of free fatty acids using *Monascus purpureus* resulted in the formation of methyl ketones, which are being produced for use as flavour chemicals. The details of the biochemical pathway that converts fatty acids to methyl ketones has been elucidated and used in large-scale fermentation processes.

Some progress has also been made in the development of bioprocesses for the manufacture of fragrances. Musks are among the most important ingredients of fragrances, but currently all the musks used are polycyclic aromatics derived from petrochemicals. Several attempts have been made to produce a musk using biotransformation. One of these involved the bioconversion of palmitic acid into ω-hydroxypalmitic acid. The yeast *Torulopsis bombicola*, which had undergone mutation to minimize beta-oxidation and ω-1 hydroxylation of palmitic acid, was able to form ω-hydroxypalmitic acid in concentrations exceeding 100 grams per litre. Cyclisation of this precursor into the hexadecanolide lactone will give a compound with musk properties. The other approach involves the conversion of C10-C18 alkanes into dicarboxylic acids by *Candida tropicalis*. Cyclisation of such precursors will also result in the formation of musk (Cheetham, 1993).

Fatty alcohols are widely distributed in nature as components of waxes. They are important products for the oleochemical industry and are produced at present by the chemical hydrogenation of fatty acids. Their biosynthesis involves the reduction of activated fatty acids in several steps by cofactor-dependent enzyme systems which are usually attached to membranes. Thus, bioreduction of fatty acids to fatty alcohols can only be carried out using intact microorganisms. Moreover, the yields are low and it seems unlikely that a commercial system will be available in the near future.

CONVERSION OF UNSATURATED FATTY ACIDS

Microbial transformation is more effective with unsaturated than with saturated fatty acids. Unsaturated fatty acids have two active sites for microbial attack, the carboxylic group and the double bond or bonds. Microbial conversion of oleic acid has produced a variety of value-added and commercially useful hydroxylated fatty acids (Hou *et al.*, 1991). The conversion is accomplished by hydration, whereby a hydrogen atom and a hydroxyl group are added to the two adjacent carbons of the olefinic bond. Also produced in the process are keto-acids, which may result from oxidation of the hydroxy fatty acids, which is presumably catalysed by other enzymes present in the microorganisms used. One hydroxy fatty acid, ricinoleic, is an important starting material for the production of sebacic acid which is used commercially in the synthesis of resins. At present, ricinoleic acid is produced commercially from castor oil.

Several microorganisms have been found to convert oleic acid to hydroxy fatty acids in high yields. Thus, *Nocardia cholesterolicum* produced 10-hydroxystearic acid with a yield exceeding 90% within six hours at pH 6.5 and 40°C (Koritala *et al.*, 1989). Minor amounts of 10-ketostearic acid were formed as a by-product. Ketostearic acid is another important starting material for making plasticizers, lubricants and detergents. In another development, *Rhodococcus rhodochrous* transformed linoleic acid to 10-hydroxy-12-octadecenoic acid as the major product and 10-keto-12-octadecenoic acid as the minor product. A total of 96% of the initial substrate was transformed using this microorganism (Litchfield and Pierce, 1986). Recently, a new bacterial strain, *Flavobacterium* sp., was found to produce only 10-ketostearic acid from oleic acid in growing cultures. A *Staphylococcus* species produced 10-ketostearic acid in 90% yield. A strain of *Alcaligenes* tolerant of high concentrations of oleic acid produced several fatty acids such as 3-hydroxyoctadec-9-enoic acid and 3,9-octadecadienoic acid from oleic acid (Esaki *et al.*, 1994a). *Bacillus pumilus* hydroxylated oleic acid to produce 15-, 16- and 17-hydroxy-9-octadecenoic acids (Lanser *et al.*, 1992).

The conversion of oleic acid to a dihydroxy fatty acid is also possible. *Pseudomonas aeruginosa* transformed oleic acid to 7,10-dihydroxy-8(E)-octadecenoic acid with a yield of 72% (Hou *et al.*, 1991). This new compound has potential use as a plasticizer and a source of intermediates in the synthesis of specialty chemicals. Recently, the biotransformation of oleic acid by *Bacillus megaterium* was found to produce octadecenamide and shorter chain fatty amides (Kanashiro *et al.*, 1994). Chemically derived fatty amides have diverse applications, such as lubricants, chemical additives, non-stick and protective coatings.

Dicarboxylic acids can also be produced by biotransformation. Thus the transformation of oleic acid and its esters by *Sarcina lutea* produced 1,7-heptanedicarboxylic acid, probably formed from oleic acid by fission at the double bonds with subsequent oxidation of an aldehyde or other intermediate (Blank *et al.*, 1991). Transformation of palmitoleic acid using *Bacillus megaterium* resulted in the production of epoxypalmitate and dihydroxypalmitate as well as monohydroxypalmitate. The soluble system from this bacterium had epoxidation and hydroxylation activity (Buchanan and Fulco, 1978; Ruettinger and Fulco, 1981).

CONVERSION OF GLYCEROL

Glycerol which is one of the products formed by the hydrolysis of fats (and some forms of transesterification) can also be subjected to biotransformation. It can replace glucose and other carbohydrates as a carbon and energy source in fermentation processes and a number of possibilities exist for the microbial conversion of glycerol into potentially higher value-added materials. Among the fermentation products obtained from glycerol are dihydroxyacetone, 1,3-propanediol, 3-hydroxypropyl aldehyde, 3-hydroxypropionic acid, pyruvic acid and glyceraldehyde (Baumann *et al.*, 1988). The first two compounds have been extensively researched and efficient systems for their synthesis developed (Houmann *et al.,* 1990; Yamada *et al.*, 1979).

MUTATION TECHNOLOGY

Changes in the fatty acid chain can be achieved using microbial cells that have undergone mutation, and mutation can also be used to block the degradation of fatty acids via the beta-oxidation pathway, thus preventing loss of the substrate. If such mutated cells are used for the biotransformation of fatty acids, then partial oxidation of the fatty acids should be found, and the products would include dicarboxylic acids. Unsaturated fatty acids can also be produced using mutated microbes. Mutation of *Rhodococcus* by irradiation with ultraviolet light endowed it with the capacity to desaturate fatty acids (Kimura *et al.*, 1991). A mutant strain of *Rhodococcus* sp. was able to *cis*-desaturate long chain alkanes, halogenated alkanes and acyl fatty acids at the central position of the chain. The acyl hexadecanoate was transformed to acyl-*cis*-6-hexadecenoates (Takeuchi *et al.*, 1990). These unusual fatty acids are said to have particular application as ingredients for cosmetics, but the ability to introduce double bonds at specific locations in the fatty acid chain may have more general applications in the oleochemical industry. Another mutant, derived from *Candida tropicalis,* was found to convert oleyl alcohol, oleic acid and methyl oleate to 9-*cis*-1,18-octadecenedioic acid through either the diterminal oxidation of alcohol or the ω-oxidation of the terminal methyl group of the mono acid (Yi and Rehm, 1989).

CONCLUSION

Microbial transformations can selectively introduce functional groups at certain non-activated positions in a molecule. Many microorganisms have the potential to produce novel fatty acids and they can adapt to a wide variety of environments. Some can survive or grow under extreme conditions such as high temperature and extreme pH. A few microbes are capable of producing unique enzymes stable towards heat, acid and alkali. Thus, there must be more ways than one can imagine of using microorganisms for the production of useful compounds. This technology should therefore be exploited to devise new products for palm oil industry, particularly oleochemicals. In future, biotransformation technology will make available to the industry differentiated oleochemicals based on their functional properties. ■

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lends further support to the neutrality of palmitic acid. At the same time it also highlights the need to reassess the classical saturated fat-lipid hypothesis and its role in lipoprotein regulation.

It must not however be assumed that all dietary saturated fatty acids are identical in their cholesterolemic effect compared to palmitic acid. There are of course some investigators who are skeptical of the neutrality of palmitic acid. The fallacies of some of the studies reporting that cholesterol levels are raised by a palm oil diet have been exposed earlier and refuted by well controlled and designed studies (Khosla and Sundram, 1996).

One has to be aware that interpretation of data is complicated when the natural organisation of triglycerides is modified in certain ways. In the long term, complete understanding of the fatty acids and their molecular orientation in triglycerides as they apply to palm oil are critical to understanding palm oil metabolism by humans. Several areas require continued efforts to improve our understanding of fatty acids relationships that distinguish palm oil from other oils. Understanding the ability of fatty acids to impact cholesterol metabolism would continue to constitute an important area of nutrition research.

PALM OIL, LIPOPROTEIN METABOLISM AND ATHEROSCLEROSIS

Dr. A.J.S. Benade and his co-workers at the South African Medical Research Council shared with us the considerable experience of his centre with the African Green monkey as a model for studying the effects of dietary lipids on lipoprotein metabolism and atherosclerosis. They also pointed out the flaws associated with loading diets with cholesterol and saturated fats for speeding up of results and its unsuitability as a model for human atherosclerosis. Dietary manipulation in the African green monkey is simple, relatively inexpensive and offers unlimited options for dietary intervention studies. PORIM are exploring this opportunity for collaborative studies on the effects of a palm oil diet on plasma lipoproteins and atherosclerosis.

Dr. Kalyana Sundram and Prof. R. Pathmanathan of the University of Malaya studying the effect of dietary saturated and trans fatty acids enriched oil blends on atherosclerosis in rabbits demonstrated adverse lipoprotein changes in trans fed rabbits. There were no atherosclerotic lesions evident in rabbits fed a high fat diet (including palm oil) but without cholesterol loading. These studies lend credence to the favourable effects of palm oil on blood lipids and atherosclerosis compared to the adverse effects of trans fatty acids.

THERAPEUTIC USES OF PALM OIL VITAMIN E (PALMVITEE)

Dr. M.L. Bierenbaum and his team from the Kenneth L. Jordan Research Group in New Jersey, USA reported on the beneficial effects of tocotrienols (palmvitee) in patients with carotid artery atherosclerosis over a period of two years. They were able to record regression of atherosclerotic lesions using bilateral duplex ultrasonography but without a concomitant reduction in serum lipid levels. The therapeutic role of vitamin E from palm oil (palmvitee) in the management of carotid stenosis needs to be explored further. Since the antioxidants have been identified as protective nutritional factors, perhaps the entire range of carotenoids in palm oil should also be considered for possible therapeutic benefits.

Dr. A.A. Qureshi and colleagues from the University of Wisconsin, Madison, USA and Armed Forces Institute of Pathology, Pakistan reported on the use of tocotrienols along with lovastatin in the management of hypercholesterolemia. They observed that tocotrienols have a synergistic effect with lovastatin in lowering serum lipids in subjects with controlled intake of fat and cholesterol (AHA step I diet). These beneficial effects, however, were not seen in free living subjects without any dietary restrictions.

Prof. Khor Hun Teik of the University of Malaya, using pure tocotrienols and a palm oil diet observed a hypocholesterolemic response in hamsters which was dose dependent. A similar response to squalene was also recorded.

Dr. M.G. Traber and Prof. Lester Packer of the University of California at Berkeley, with a sensitive technique for detection of tocotrienols and tocopherols pointed out the selective concentration of tocotrienols in the skin. This suggests that tocotrienols may offer protection against environmental stresses. They were able to demonstrate its protective role against UV radiation in the hairless mice.

Dr. M.Y. Abeywardena of the CSIRO, Australia studying blood vessel dysfunction, focussed on the modulation of vascular endothelial function by palm oil antioxidants. Vascular endothelial function is affected by ageing, hypertension and hyperlipidemia. Natural anti-oxidants confer benefits against cardiovascular disease and the minor constituents in palm oil have a modulatory role.

CORONARY HEART DISEASE (CHD)

Neither cholesterol nor heart disease has an isolated existence. As such, searching for a single cause of hypercholesterolemia in saturated fats is frightening to say the least. Many dietary constituents and confounding factors influence the risk of CHD. It is important to recognise the interplay between dietary, genetic and lifestyle factors that influence the development of not only CHD but also hypertension.

The management of hyperlipidemias and hypertension should be targeted at overall risk and not simply at cholesterol or blood pressure. The obsession with saturated fats and their hypercholesterolemic effects detracts from treatment of more important risk factors such as smoking, inactivity and from sensible dietary practices based on current scientific knowledge.

Many important questions about the best approach to the dietary prevention of CHD remains to be answered and without doubt, much more nutritional research is needed before the optimal diet can be determined.

TOCOTRIENOLS AND EXPERIMENTAL CARCINOGENESIS

The minor constituents of palm oil, namely the tocotrienols have been investigated for potential anti-cancer properties by a number of investigators. Prof. K.K. Carroll of the University of Western Ontario, Canada reported synergistic effects between tocotrienols, flavonoids from various plant sources and tomoxifen in inhibiting human breast cancer cells *in vitro*. They had shown earlier that tocotrienols inhibit proliferation and growth of breast cancer cells *in vitro*.

Dr. A.A. Qureshi and C.E. Elson of the University of Wisconsin, Madison, USA reported that tocotrienols suppress tumor development in animals treated with carcinogens and extend the life of animals following tumor transplant. They also suppress the proliferation of cultured tumor cells *i.e.* B16 melanoma cells and this was dose dependent with delta and didesmethyl tocotrienols being more potent than the other tocotrienols.

Dr. Permeen Yusof of Universiti Kebangsaan Malaysia noted that tocotrienols inhibit the proliferation of hematopoietic cells expressing cytokine receptors *in vitro*. Dr. Wan Zurinah from the same University recorded that the severity of experimental hepatocarcinogenesis is lessened by simultaneous administration of palm vitamin E as assessed by enzyme activities.

RED PALM OIL IN THE PREVENTION OF VITAMIN A DEFICIENCY

Vitamin A deficiency continues to be a problem in many developing countries. Dr. R. Manorama and associates from the Andhra Pradesh Agricultural University have once again shown the efficacy of utilizing red palm oil as a source of β-carotene in combating vitamin A deficiency in school children. By incorporating red palm oil as a supplement in normal snacks, they observed improvements in the serum retinol levels and liver storage of vitamin A.

Dr. L.M. Canfield and colleagues of the University of Arizona and colleagues from Honduras have further confirmed the usefulness of red palm oil as a vitamin A supplement for lactating mothers and thereby improving the vitamin A status of nursing infants. They demonstrated convincingly elevations in the serum retinol levels in both mothers and infants after incorporating red palm oil into the diets of lactating mothers.

The above two studies illustrate the efficacy of red palm oil with its high β-carotene content in enhancing the vitamin A status of lactating mothers, nursing infants and school children.

As such it is imperative that this potential be harnessed as a cost effective way of reducing morbidity and mortality amongst children in developing countries. The approach proposed if aggressively pursued would benefit the unfortunate in developing countries. The current practice of administration of massive doses of vitamin A to children and promoting consumption of green vegetables has not been successful and has its limitations. In this connection it is encouraging to note that red palm oil has captured the attention of researchers and to a lesser extent the policy makers as a practical dietary solution to combat the scourge of vitamin A deficiency.

PALM OIL AND OBESITY

Dr. D.B. Hausman *et al.* from the University of Georgia, USA presented current concepts regarding the association between obesity and macro nutrient balance. They then reported on the influence of dietary fat type on adipose tissue expansion and obesity in rats. There was a depression in fat storage in rats fed a palm oil diet compared to soyabean oil or tallow. This anti obesity effect has been attributed to a slower rate of triglyceride uptake by adipose tissues and/or a reduced fat cell proliferative capacity. There were no significant effects of dietary fat types on serum lipids.

In industrialised countries eating patterns present a metabolic stress due to over-consumption of fat exacerbated by the high energy of the food. Alcohol is widely consumed in addition to food and it increases energy imbalance, promotes visceral obesity and has synergistic effects with fat intake. This abnormal fat imbalance is probably the major contributor to the present epidemic of obesity. The increase in body weight is accompanied by a rise in production of VLDL and LDL and a reduction in HDL thereby contributing to CHD risk. Obesity is increasing in developed countries and the immense economic and social burden of obesity is indeed worrying. The proportion of obese people in the United States of America is around 30% and continues to rise. The health care costs related to obesity in the United States was US$39 billion in 1986 and another US$30 billion is spent annually on efforts to control or lose weight. If everyone were to consume an optimal diet, we would have a much greater chance to reduce avoidable illness.

PALM OIL ASSISTS IN PROTEIN UTILISATION

Dr. C.J.K. Henry of the Oxford Brookes University, United Kingdom stressed the importance of the nature of dietary fat type on protein utilisation. The net protein utilisation of rats given refined palm oil was significantly better than that of rats given other palm oil fractions or oils. This observation has relevance to the rehabilitation of children with protein calorie malnutrition especially in countries afflicted by the ravages of civil disturbances, natural calamities and punishing sanctions.

PALM OIL AND PEROXIDATIVE DAMAGE

Dr. Amin Nanji of the Harvard Medical School, Boston, has shown that palm oil is able to reverse some of the changes in the liver induced by alcohol in rats. He attributed this benefit to the composition of palm oil in terms of its fatty acids and minor constituents. A palm oil based strategy for managing clinical alcoholic liver disease is suggested as an interesting possibility.

CONCLUSION

Research on the nutritional aspects of palm oil has been active. Evidence collected since the previous conference further reinforces the versatile role of palm oil and its constituents in nutrition and health. On the whole the presentations and deliberations were useful in enhancing the positive attributes of palm oil. It was very reassuring to note that no detrimental effects of palm oil has been reported in any of the presentations. The progress made since the last conference was remarkable. Many of the findings are exciting. Some of them confirm what is generally known, others provide answers to the mechanisms involved and a few unravel future potentials for the use of palm oil. This conference has also helped us keep ourselves abreast of current knowledge in science and technology and encouraged us to interact.

Some of the work presented was in preliminary form. The results of some investigations are being processed for publication in peer reviewed journals as this would have a major impact on the scientific community. It would certainly provide more credibility to the research and also stimulate further research on the effects of palm oil, palmitic acid and the minor constituents such as tocotrienols and carotenoids. The research data would be utilised to enhance the image of palm oil further.

The conference culminated with a dialogue on future directions for research on palm oil nutrition. Basic research on palm oil has contributed very much to our understanding of the effects of palm oil in human nutrition. It was also evident that there is a growing demand for more research as there remains much more to be done. Many issues have to be attended to on a priority basis to enhance our R&D capabilities. The formula for ensuring success is simple, namely; direction, values and continuous improvement. ■

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