

Research report

The Salvestrol Concept helps to explain how a group of naturally-occurring plant compounds work to prevent cancer and also offer a treatment for cancer with far fewer side effects than conventional chemotherapy.

Salvestrols

NATURAL PLANT-DERIVED ANTICANCER AGENTS?

*By Professor Dan Burke and
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EATING fruit, vegetables and herbs is good for our health. Many members of the public, a majority of the medical and healing professions, many scientists and several governments all accept this, and medical advice is to eat at least five portions of fruit or vegetables each day.

The medical and scientific evidence shows that a diet rich in fruit and vegetables helps to combat not only cancer, but other diseases. Exactly how do fruit, vegetables and herbs ward off cancer? And how can we maximise this protection? There is probably more than just one single mechanism whereby plants are able to act against human cancer, and although there are several scientifically researched and published theories, we have no definitive answers.

It is also the case that conventional chemotherapy against cancer, using synthetic drugs, is beset by widespread and severely debilitating side effects.

A team of research scientists and natural products specialists in Leicester believe that a group of natural plant compounds called Salvestrols may provide part of the answer. They believe that Salvestrols can, on the one hand, help to explain how plants prevent cancer, and on the other offer a treatment for cancer with far fewer side effects.

The Salvestrol Concept explains how the body defends and heals itself from cancer, using natural plant compounds in the diet and a special enzyme in cancer cells. It is based on the combined research of Professor Gerry Potter, a medicinal chemist, and Professor Dan Burke, a pharmacologist, together with Nature's Defence (UK) Ltd (a manufacturer of natural products).

Salvestrols are a new class of natural anticancer chemicals, which are found in plants and safely eaten in the diet. Initially non-toxic to the body's normal cells, Salvestrols become activated inside human cancer cells by an enzyme, CYP1B1 (pronounced "sip one bee one").

The activated Salvestrols then cause the cancer cells to stop growing or die, without harming normal cells. This specificity of action is possible because CYP1B1 is an intrinsic component of cancer cells and occurs in all of the wide range of different types of cancer that have been studied to date, but is to all intents and purposes absent from normal cells.

Modern agriculture minimises Salvestrols

Salvestrols are not a single chemical type of plant compound, but are defined on the basis of their mechanism of anticancer action as summarised above. Moreover, it is now clear that several food plants and plant-rich diets that have traditionally been considered to offer protection against cancer can be good sources of Salvestrols.

For example, Salvestrols can be particularly high in many red or green health-giving plant species, including fruit, berries, vegetables and herbs. Good natural sources of Salvestrols include strawberries, cranberries, oranges, tangerines and grapes. Olives are also a good source of Salvestrols. Several herbs contain appreciable levels of Salvestrols, including basil, parsley, sage, rosemary, thyme, mint, artichoke, scutellaria and the roots of milk thistle and dandelion.

Unfortunately, modern agricultural practices have succeeded in minimising the levels of Salvestrols in fruits and vegetables through a combination of the development of modern plant

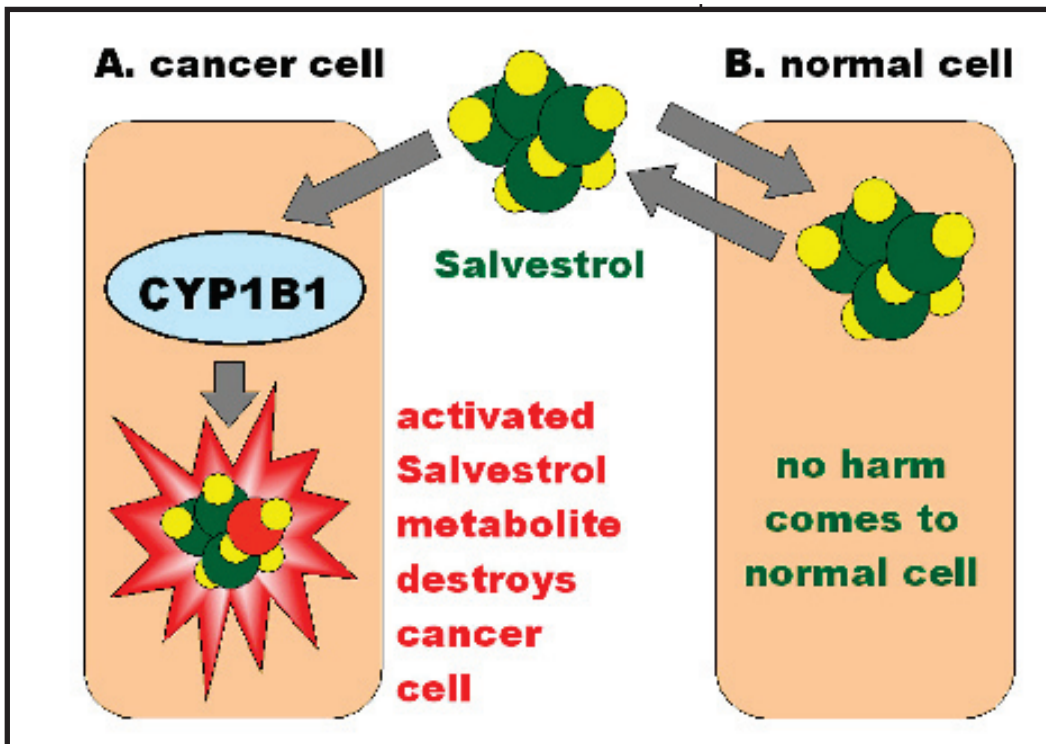


Figure 1: The Salvestrol Concept

(A) In a cancer cell: a Salvestrol molecule in the bloodstream diffuses into the cell where it is metabolised by the CYP1B1 enzyme into a Salvestrol metabolite molecule, which poisons the cancer cell. (B) in a Healthy Cell: a Salvestrol molecule diffuses into the cell but, because CYP1B1 is absent, the Salvestrol is not converted into a metabolite and diffuses back into the bloodstream without harming the healthy cell.

varieties, the use of agrochemical crop sprays and the selective processing of harvested fruit. Recent research into the sources of Salvestrols has revealed that levels of these compounds are up to 30-fold higher in organic produce.

A main reason why fruits produce Salvestrols is that many of these compounds are natural antipathogenic agents, which the plants produce to protect themselves in response to an attack by pathogens.

However, when fruit crops are routinely sprayed with synthetic agrochemicals they rarely get attacked by the pathogens and so lack the main stimulus to produce Salvestrols.

Bitter taste

Many Salvestrols are bitter tasting and for this reason they are sometimes deliberately removed by manufacturers from fruit juice. Salvestrols generally do not dissolve readily in water and so are found more in the skins, pulp and stones of fruit rather than in the pure juice. Consequently, when fruit juices are clarified much of their Salvestrol content is removed.

Furthermore, traditional wine-making techniques, which ban the use of agrochemicals on the vines and ferment the grapes in contact with their skins, tend to give higher levels of Salvestrols in the ensuing wine compared to modern winemaking techniques, in which the pulp of grapes from agrochemical-treated vines is separated from the skins before fermentation.

This is because (i) the presence of pathogens encourages the grapes to produce Salvestrols and (ii) the alcohol that is formed during the fermentation process dissolves the Salvestrols out of the grape skins (Salvestrols being poorly soluble in water).

For different reasons, traditionally milled cloudy olive oil often has higher levels of Salvestrols than clear oil produced using modern methods.

Older varieties of several fruits have higher Salvestrol contents than newer varieties. This is probably because the newer varieties have been selected for their sweeter taste (Salvestrols are bitter-tasting) and any greater susceptibility to pathogens (due to their lower Salvestrol levels) is overcome by modern agrochemical-dependent methods of agriculture.

The salvestrol concept

The Salvestrol Concept is firmly based on extensive scientific research, spanning a period of more than ten years. In the early 1990s Professor Burke's research group found that a certain enzyme protein, called CYP1B1, was clearly

present in the tumour cells of a wide variety of human cancers, but was undetectable in the normal cells of the corresponding healthy tissues.¹

The technical description for this is that CYP1B1 is highly overexpressed in cancer cells. This has since been confirmed by a number of eminent laboratories across the world, including the United States and Japan.^{2,3} Then around the year 2000 Professor Potter, working with Professor Burke, discovered that, through a metabolic process, CYP1B1 brings about a subtle change in the chemical structures of certain plant compounds and that the metabolites are potent anticancer toxins.⁴

In this process of activation, the anticancer effects are due, not directly to the actual plant chemicals, but to the metabolites which are generated in the human cancer cells.

Finally, in an inspirational moment, Professor Potter realised that this could help explain how many different types of plants combat cancer and how many plant compounds that were previously thought to be without direct anticancer activity could, indeed, be able to attack cancer cells. He coined the term "Salvestrols" to describe plant chemicals that are activated against cancer in this way.

Summary

Thus, to summarise, there are three components to the Salvestrol concept:

1. Salvestrols – the natural, plant-based chemicals
2. CYP1B1 – the special enzyme that is uniquely intrinsic to cancer cells

3. Salvestrol metabolites – the activated anticancer toxins.

Salvestrols are taken in the diet. When Salvestrols encounter human cancer cells they are absorbed into the cells, where CYP1B1 activates them by converting them into slightly different chemicals – the Salvestrol metabolites, which then act to poison the cancer cell. Normal cells generally lack CYP1B1, so although Salvestrols are absorbed into normal cells they are not converted into active metabolites. Thus, the normal cells are not poisoned and the Salvestrols are excreted from the normal cells unaltered. This is shown diagrammatically in Figure 1.

Several natural chemicals and synthetic medicinal drugs other than Salvestrols can become activated in healthy tissues of the body (although not by CYP1B1). However, the key feature of Salvestrols is that they are activated only inside the cancer cells which they then arrest or kill, and not in healthy cells. And although there are hundreds of different enzymes which are ubiquitous in the body, CYP1B1 is virtually confined to cancer cells.

Salvestrols are currently identified by testing plant compounds against CYP1B1-containing human cancer cells and non-CYP1B1-containing human cells, in culture in the laboratory.

By definition, Salvestrols kill CYP1B1-containing cells in preference to cells that lack CYP1B1. The first Salvestrol to be identified was resveratrol, a chemical from grapes that is notably present in red wine and which is widely credited with cancer prevention properties.

Resveratrol is metabolised by CYP1B1 into a metabolite, piceatannol, which is a known anticancer toxin.⁴ Other, more powerful Salvestrols have since been identified in a wide variety of fruits, including tangerines, strawberries and cranberries. The results for a typical Salvestrol, codenamed Q40, are shown in Figure 2.

Human cells in culture were treated with a range of Q40 concentrations and then the number of cells surviving at each concentration was measured under a microscope. By definition, 100 per cent of the cells survived when no Q40 was added.

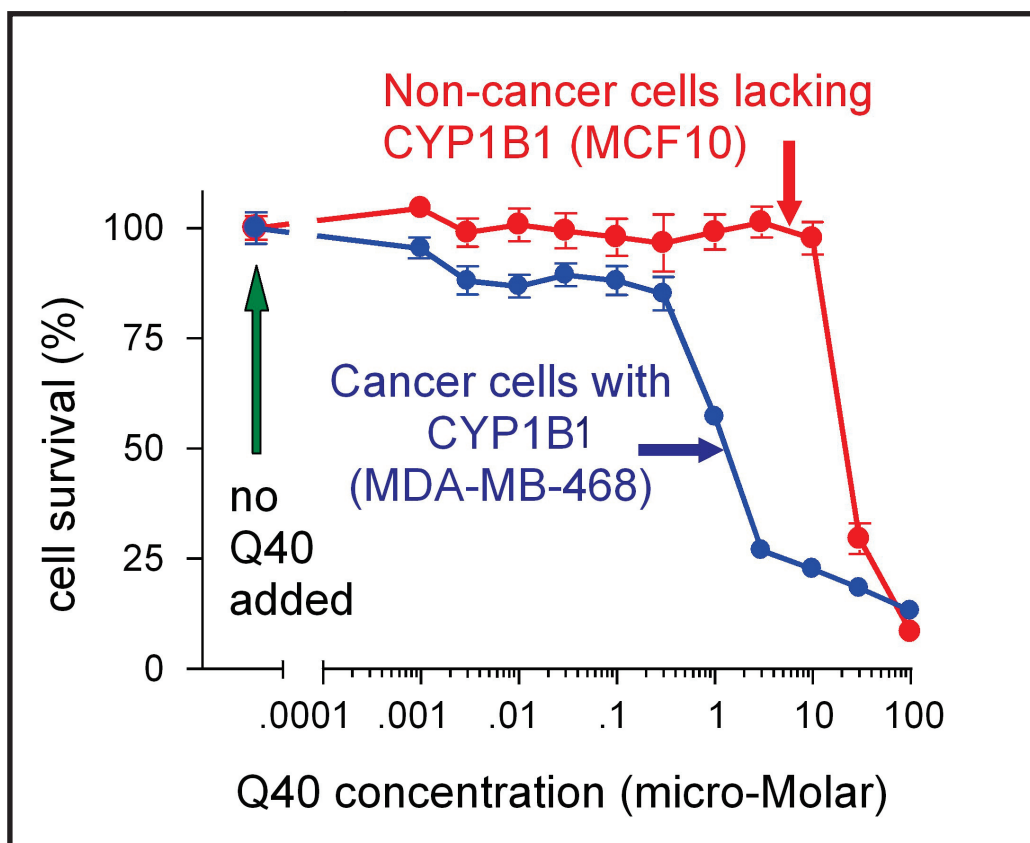


Figure 2: Salvestrol Q40 toxicity to cells with or without CYP1B1

Human breast cancer cells containing CYP1B1 (MDA-MB-468) and human cells lacking CYP1B1 (MCF10) were each treated with a range of concentrations of Q40 (horizontal axis) and the percentage of cells surviving at each concentration was measured under a microscope (vertical axis).

The results are mean values of four determinations \pm standard error of the mean (sem). Note that the horizontal axis is logarithmic, i.e. each major division represents a 10-fold range of Q40 concentrations, e.g. 0.1–1, 1–10, 10–100 etc. The Q40 concentration that killed 50 per cent of cells was 10 times lower for the CYP1B1-containing cells than for the CYP1B1-lacking cells.

The results show that breast cancer cells which contain CYP1B1 (MDA-MB-468 cells) were killed at a very low concentration of Q40, and at a much lower Q40 concentration than cells that lack CYP1B1 (MCF10 cells).

(All chemicals kill any cells if used at a high enough concentration, but the concentration needed to kill CYP1B1-lacking cells could never be achieved in practice in living people).

These results show that Salvestrol Q40 is a highly selective killer of CYP1B1-containing cells.

The search for powerful Salvestrols focuses on compounds with the twin attributes of (i) killing CYP1B1-containing cancer cells at a very low concentration and (ii) showing a very large difference between the concentration able to kill CYP1B1-containing cells and a higher concentration needed to kill CYP1B1-lacking cells.

The Salvestrol Concept deems CYP1B1 to be a tumour suppressor and rescue mechanism, which has evolved to enable the body to defend and heal itself against cancer by activating some of the natural compounds found in edible fruits and other dietary plants.

CYP1B1 is present in the cells of all the different types of

cancer that have been investigated to date, including all the most prevalent cancers, for example bladder, brain, breast, colon, oesophagus, kidney, liver, lung, lymph node, ovary, skin, stomach, testis and uterus. CYP1B1 can be thought of as a Trojan Horse inside the cancer cells, which merely has to be provided with Salvestrols in the diet in order to unleash a stream of chemical agents that are deadly to the cancer cells. In other words, in CYP1B1 the body seems to have provided cancer cells with the seeds of their own destruction.

Cancer scientists generally believe that single cancer cells are continually forming in the human body and that most of these are destroyed by the body before they develop into malignant tumours.

Salvestrols in the diet are a mechanism by which this ongoing prevention of cancer can occur.

In terms of cancer treatment, most current anticancer chemotherapy is beset by serious side effects. These occur because most anticancer drugs are cell poisons that do not distinguish between cancer cells and many types of healthy cells. Because Salvestrols are activated into anticancer toxins only within cancer cells, they offer the possibility of anticancer treatment without the awful side effects.

Unfortunately, because of modern varieties and the use of synthetic agrochemicals and post-harvest manufacturing techniques, simply eating fresh or processed fruit probably provides us with much less Salvestrols than we expect.

For more information see www.naturesdefence.com and www.fruitforce.co.uk

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