

## REVIEW ARTICLE

# The contribution of homeogenomic and homeogenetic studies in the support of the practice of Homoeopathy

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### ABSTRACT

Almost two decades ago, it was postulated that homoeopathic remedies could deliver their benefits by interacting with the genetic blueprint. Over the years, the results of many homeogenomic gene expression studies have confirmed this postulate. The results of homeogenomic studies have begun to recognize which of the estimated 25,000 human genes are targeted by different homoeopathic remedies and how the expression profiles of these targeted genes are rearranged. From a mechanistic standpoint, seminal homeogenomic studies have shown that homoeopathic remedies can also facilitate epigenetic modifications such as DNA methylation. This is an important discovery because DNA methylation plays an important role in the control of the expression of many genes. Understanding of the genes targeted by different homoeopathic remedies, taken together with information about the function of the protein/s encoded by the targeted gene/s provides a further complementary approach to homoeopathic remedy selection. In this review, as an example, we show how the results of homeogenomic studies support the applicability of frequently used homoeopathic remedies in patients suffering from cancer, particularly with respect to upregulation of the gene TP53. This review also outlines how the results of homeogenomic studies may also provide further help with potency selection and optimum dosage regimen.

**Keywords:** Gene expression, Homeogenetics, Homeogenomics, Homoeopathy

### INTRODUCTION

Homoeopathy was developed around two centuries ago by Dr. Samuel Hahnemann. Its health care benefits are delivered more frequently by administration of highly diluted potentized substances, or remedies although crude forms (mother tinctures) are occasionally used depending on certain conditions of the patient.

There are many remedies used presently. To select which one of these remedies is most appropriate for any particular patient, practitioners use a number of different ways to select the most suitable remedy, as outlined below.

### The *Similimum*

According to the basic principle of Homoeopathy, "like-cures-like," remedy selection is based on the pattern of symptoms presented by the patient. The

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homoeopath then chooses the appropriate remedy by reference to the results of a remedy proving. The appropriate remedy is the one that matches a set of symptoms that is generated when the same remedy is administered to healthy subjects. Symptom patterns developed in healthy subjects as part of the proving process are detailed in various Repertories.

Over many years, there have been many different Repertories assembled by notable practitioners such as James Tyler Kent, William Boericke, Clemens Von Boenninghausen, and many others. One of the most recent and popular Repertories has been compiled by Frederik Schroyens. A list of many different recognized repertories has been compiled by Srivastav.<sup>[1]</sup>

Although most of remedies have been subjected to proving process, a host of symptoms have been derived from toxicology studies and reports of poisonings.

Clearly, reference to each of the different repertories or other remedy selection criteria has the potential to affect the selection of the most appropriate remedy for any particular patient.

## HOMEOGENOMICS AND HOMEOGENETICS

A further future approach to remedy selection, introduced in this review, takes into account the results of many years of homeogenomic studies. In the absence of pharmacological intervention, it is now clear that many homoeopathic remedies influence the biological or psychological phenotype of an individual by rearranging the expression of many genes.

### What is Homeogenomics?

The term homeogenomics refers to studies that focus on understanding more about the interactions between homoeopathic remedies and the genetic blueprint or genome. Such studies involve identification of which gene or genes are targeted by a particular remedy. Homeogenomic studies also refer to investigations designed to reveal epigenetic modifications that are associated with rearrangement of the expression of targeted gene/s.<sup>[2]</sup>

### What is Homeogenetics?

Homeogenetics refers to studies which are needed to investigate the ways in which different inherited forms of genes interact with the substance or remedy being administered. Homeogenetic studies may be

more relevant with respect to the administration of mother tinctures or less diluted remedies. Such future studies have the potential to reveal how differences in the genetic makeup of an individual may influence the effectiveness of a remedy in any particular patient.

(The proposed terms homeogenomics and homeogenetics are in keeping with the accepted terms pharmacogenomics/genetics and nutrigenomics/genetics which refer to studies that investigate the interaction between pharmacologically active substances and food components, respectively, with the genetic blueprint).

The study of homeogenomics began formally almost two decades ago<sup>[3]</sup> when one of us (A R K-B) first postulated that homoeopathic remedies would have the capacity to interact with the genome and rearrange the expression of many genes. Since that time, the results of many investigations have confirmed this postulate.<sup>[4]</sup>

It is now known that individual homoeopathic remedies can rearrange the expression of many genes.<sup>[4-7]</sup> Some genes are upregulated, whereas other genes are downregulated. For example, Marzotto *et al.*<sup>[7]</sup> have discovered that the homoeopathic drug derived from *Gelsemium sempervirens* has the capacity to upregulate the expression of at least six different genes as well as downregulate the expression of almost fifty different genes.

Because so many homoeopathic drug/genome interactions have been reported thus far, the usefulness of homeogenomic findings in the support of remedy selection is exemplified by reference to work which has identified remedies that promote the expression of the gene *TP53*. This serves only as one good example among many such other genes that not only act as “tumor suppressor” genes like that of *TP53* but also because *TP53* has also a unique function to subserve as a “gate-keeper” gene. It guides cancer cells if they should be guided toward their death (apoptosis). Alternatively, they can be given a chance to repair/restore to the extent that they cannot any more allow abnormalities/breaks/damages in DNA to perpetuate in daughter cells.

### About *TP53*

The gene *TP53* encodes the protein p53. From a health standpoint, p53 is arguably one of the most biologically important protein molecule found so far.

It plays an important role in many critical biological events including development and progression of cancer.<sup>[8]</sup>

### TP53 AND CANCER

There are many causes of cancer. However, damage to DNA, particularly to genes that control the cell cycle is one of the major pathways.

It has been found that p53 works in a number of different ways to resolve cancer.<sup>[8]</sup> It plays a role in apoptosis (programmed cell death), genomic stability (DNA repair), and inhibition of angiogenesis (prohibiting formation of blood supply to the tumor) and inhibition of activity of an enzyme called telomerase in cancer cells.

As indicated above, the product of the *TP53* gene can activate DNA repair proteins when DNA of a tumor suppressor gene, for example, has been damaged. It can also slow down the cell cycle so that the DNA repair system that it has activated has time to repair the damage. If p53 decides that the damage to DNA is beyond repair, it has the remarkable property of instructing the cell to commit suicide by a process called apoptosis or programmed cell death. It does this by activating a system that enables the cell to kill itself by destroying its own DNA.<sup>[8]</sup> It plays an important role in killing cancer cells in which DNA has been irreparably damaged by chemotherapy and radiotherapy.

For a tumor to grow, it needs an adequate blood supply. p53 is able to restrict the development of tumor's blood supply, prohibit angiogenesis so that its growth is impaired.

As cells divide, the ends of chromosomes shorten until they lose the capacity to divide. There is an enzyme called telomerase that repairs the shortened chromosomes so that cells can continue dividing. In this way, excessive telomerase activity, often found in some cancer cells help them to grow. p53 also helps to slow down the growth of tumors by inhibiting the activity of telomerase in cancer cells.<sup>[8]</sup>

### TP53 AND HOMEOMIC STUDIES

Because of the significance of the role of diminished p53 activity in development and progression of a wide range of different types of cancer, many homeomic studies have focused on

identification of remedies that have the capacity to support the expression of *TP53*. This review describes some of them that have been performed in the laboratory on living cell lines (*in vitro*) or on animal models (*in vivo*).

#### In Vitro Studies

Many *in vitro* studies have been designed to determine whether homeopathic remedies have the capacity to promote the expression of *TP53*. For example, Ghosh *et al.*<sup>[9]</sup> demonstrated that a mother tincture prepared from *Phytolacca decandra* could promote the expression of *TP53*, as well as other apoptosis supporting genes such as *BAX* and the gene that encodes caspase-3 in cells derived from a human malignant melanoma. As might be expected, these scientists also demonstrated that *Phytolacca decandra* could readily induce apoptosis in these cells. Importantly, this study showed that normal human peripheral blood leukocytes were less affected by this remedy indicating that neoplastic cells are more susceptible to p53- induced apoptotic cell death compared to healthy cells when exposed to a concentrated form of *Phytolacca decandra*.

Further, the Condurango-glycoside-A fraction extracted from *Gonolobus condurango* was found to induce DNA damage associated cell senescence and apoptosis via a reactive oxygen species (ROS)-dependent p53 signaling pathway in HeLa cells.<sup>[10]</sup>

Other workers<sup>[11]</sup> have shown that the homeopathic remedy *Carcinosinum* at 200C is able to promote the expression of *TP53* in neoplastic cells of lymphoid origin. The remedies *Thuja occidentalis* and *Ruta graveolens* in the same potency do not appear to have the capacity to do this. Similar findings have been reported by Preethi *et al.*<sup>[12]</sup> However, the main active compound flavonol isolated from the leaves of *Thuja occidentalis* was shown to have the ability to arrest the cell cycle of human lung cancer-derived cells (A549) by an ROS-independent apoptotic pathway.<sup>[13]</sup> Similarly, lycopodine, the active biological ingredient of a homeopathic mother tincture prepared from *Lycopodium clavatum* was shown to trigger apoptosis by another signaling pathway. It was shown to do this by modulating 5-lipoxygenase activity and depolarizing the membrane potential in androgen sensitive and refractory prostate cancer cells without actually modulating p53 activity.<sup>[14]</sup> Thus, it is important

to note that *in vitro* homeogenomic studies have revealed that homoeopathic remedies can promote programmed cell death of various neoplastic cells by quite different apoptotic pathways that do not always require the contribution of p53.

Interestingly, since Smits<sup>[15]</sup> has identified that there are at least eight different compositions of *Carcinosinum* in use, some of which have quite different clinical properties, it would be helpful to subject each of these different *Carcinosinum* preparations to similar homeogenomic studies. Results of such studies would help to understand more about the gene targeting specificity of the contents of different remedies.

### **In Vivo Studies**

As indicated, *in vitro* studies have the potential to determine the specificity of genes targeted by individual remedies. On the other hand, *in vivo* homeogenomic studies have the capacity to provide further information such as the optimum potency and dosage regimen to use. For example, in the case of *Calcarea carbonica*, Saha *et al.*<sup>[16]</sup> have shown that, in a mouse cancer model, twice daily administration of a 6C potency of this remedy for a period of almost 4 weeks killed implanted neoplastic cells by a p53 dependent pathway. This pathway required the contribution of an intact immune system including cytotoxic T-cells. Interestingly, in the same study, the neoplastic cell cytotoxic effects of *Calcarea carbonica* were not observed when the same remedy was used in potencies of 12C, 30C, or 200C.

Further, *in vivo* studies have shown in an animal model of lung cancer<sup>[17]</sup> that following administration of a stock solution of *Marsdenia condurango*, (an extract of which is used to prepare a homoeopathic remedy),<sup>[18]</sup> the progression of lung cancer in rats was significantly slowed down. The expression of the *TP53* gene was increased concomitantly after treatment with this remedy twice daily over a period of months.

## **HOMEOGENOMIC STUDIES AND DNA METHYLATION**

Having established that homoeopathic remedies have the capacity to rearrange the expression profile of many genes; investigations have been initiated to determine how these changes may be brought about. Various ways are known by which the expression of a gene can be modulated. One of the ways is by an epigenetic process called DNA methylation.<sup>[2]</sup>

DNA methylation refers to the addition of methyl groups to cytosine nucleotides within DNA. Addition of methyl groups to DNA plays a role in suppression of the expression of a gene. By contrast, removal of methyl groups from DNA (demethylation) is associated with the ability to express the gene. Maintenance of the correct methylation status of the full complement of genes is needed for a cell to function properly.

It has been known for many years that disturbances in the methylation status of the genome are strongly associated with development and progression of cancer.<sup>[19]</sup> Epigenetic hallmarks of neoplastic cells include regional hypomethylation (an atypical reduction in methylated cytosine residues) as well as hypermethylation (an atypical increase of methylated cytosine residues) of various regions of the genome.<sup>[20]</sup>

Because *Marsdenia condurango* had been demonstrated to slow down progression of cancer *in vivo*,<sup>[17,18]</sup> the methylation status of important tumor suppressor genes such as *TP53* was examined in this model. Interestingly, the results of molecular biological studies have shown that genomic regions including tumor suppressor regions are able to be demethylated by exposure to the homoeopathic remedy *Marsdenia condurango*.<sup>[21]</sup> Evidence of an epigenetic modification resulting in cell cycle arrest caused by the use of an ultra-highly diluted remedy prepared from *Condurango* has also been documented in cancer cells *in vitro*.<sup>[22]</sup>

Bellavite *et al.*<sup>[23]</sup> also provided evidence through transcriptome analysis that highly diluted preparations of *G. sempervirens* could modify gene expression profiles of neurocyte genes. Very recently, Bigagli *et al.*<sup>[24]</sup> also reported that homoeopathic *Apis mellifica* preparations could rearrange the transcriptome in human prostate-derived cells.

Interestingly, the ability of highly diluted substances to rearrange gene expression profiles has also been demonstrated by Marotti *et al.*<sup>[25]</sup> even in wheat seedlings. Following treatment of wheat seedlings with ultra-high dilutions of arsenic trioxide (used as a homoeopathic remedy to resolve symptoms of arsenic poisoning), these workers showed that the expression of many genes was altered in a beneficial way.

These findings reveal important new insights into the ways in which homoeopathic remedies can rearrange the transcriptome to bring about their

medicinal benefits. As discussed by the authors of these latter studies,<sup>[23-25]</sup> taken together with the definitive findings by Khuda-Bukhsh and Sikdar,<sup>[21]</sup> it is becoming apparent that some homoeopathic remedies have the ability to alter the epigenetic profile of the genome. These are highly significant findings because the discovery that various homoeopathic remedies have the ability to alter the epigenetic status of the genome has important implications in control of the biological and psychological characteristics of an individual.

### OTHER INFORMATIVE HOMEOGENOMIC INVESTIGATIONS

As discussed above, the results of homeogenomic studies provide further information that may be used to optimize the application of specific remedies. For example, reference to work of Hofbauer *et al.*<sup>[26]</sup> allows the potential advantages and disadvantages of the use of the homoeopathic remedies *Nux vomica* and *Calendula officinalis* to be further explored. As indicated,<sup>[26]</sup> the remedies *Nux vomica* and *Calendula officinalis* are used to treat gastritis in general.

There are many causes of gastritis including infection with the bacterium *Helicobacter pylori*.<sup>[26]</sup> Infection of gastric epithelial tissues by *H. pylori* may lead to gastric ulceration. Hofbauer *et al.* have shown in homeogenomic studies that *Nux vomica* and *Calendula officinalis* reduce the expression of the mitogen heparin-binding epidermal growth factor (HB-EGF) in *H. pylori*-infected gastric-derived cells in culture.<sup>[26]</sup> Because increased expression of HB-EGF is associated with neoplastic transformation and tumor progression,<sup>[27]</sup> it is rational to conclude that these two remedies may help in reducing the possibility of neoplastic transformation of cells involved in *H. pylori* gastric ulceration. On the other hand, because HB-EGF plays an important role in repair of damaged gastric epithelial cells,<sup>[26]</sup> reduced expression of this important tissue repair mitogen by these two remedies may slow down the healing of *H. pylori* damaged gastric epithelial cells. Clearly, investigative studies are required to critically assess the suitability of these two remedies in cases of *H. pylori*-induced gastric ulceration.

### HOMEOGENETIC CONSIDERATIONS

As indicated above, homeogenetic studies focus on the way in which a person's genes interact with homoeopathic drugs, particularly those which

are administered as mother tinctures or in low potency or in undiluted form. It is well known that many drugs require activation by members of the cytochrome P450 system before they exhibit their beneficial effects. One of the most important members of the cytochrome P450 family involved in drug activation, CYP2D6, exists in many different genetic forms, some of which are unable to activate many drugs.<sup>[28]</sup> It is plausible that application of homeogenetic studies in the future may help to determine which remedies may be most efficacious in patients with a particular genetic background.

### CONCLUSIONS

Homeogenomic studies have confirmed the postulate<sup>[3]</sup> that homoeopathic remedies have the capacity to rearrange the transcriptome. The results of many homeogenomic studies are beginning to identify the gene targeting specificities of a number of homoeopathic remedies. The results of these studies are also providing information that can be used to optimize dosage and frequency of dosage of homoeopathic remedies. Furthermore, of major significance is the fact that homeogenomic studies are beginning to identify genes whose expression is downregulated by homoeopathic remedies. This is an important realization because many diseases are caused by increased expression of various genes such as those involved in cell cycle initiation and genes that encode a wide variety of inflammatory mediators, for example. Homoeopathic remedies that are able to reduce expression of such genes will certainly have wide clinical applications.

Information regarding the gene targeting specificity of individual homoeopathic remedies, taken together with knowledge of the function of the targeted gene/s as well as the symptom pattern caused by suboptimal or abnormally increased expression of the same gene permits a further complementary approach to remedy selection. Therefore, this new area of research warrants extensive contributions by other researchers to confirm (or refute) the possibility of developing a more personalized remedy selection procedure by application of molecular homeogenomic and homeogenetic analytical data.

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## Conflicts of Interest

There are no conflicts of interest.

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### होम्योपैथी के अभ्यास के समर्थन में होम्योजेनोमिक और होम्योजेनेटिक अध्ययनों का योगदान

लगभग दो दशक पहले यह माना जाता था कि होम्योपैथिक औषधियाँ केवल एक खास ब्लूप्रिंट के संग काम कर सकती हैं। समय के साथ कई होम्योजेनोमिक अध्ययनों ने इस विचार को पुख्ता किया है। इन अध्ययनों के परिणामों ने यह पहचानना आरंभ किया है कि लगभग 25,000 मानव गुणसूत्रों को विभिन्न होम्योपैथिक औषधियाँ लक्षित करती हैं और कैसे उनके प्रोफाइल को पुनः व्यवस्थित किया जाता है। इन अध्ययनों ने यह भी पहचाना है कि कैसे कुछ होम्योपैथिक औषधियाँ एपीजेनेटिक संशोधन जैसे कि स्वास्थ्य को बढ़ावा देने वाले विभिन्न जीनस की अभिव्यक्ति प्रोफाइल में परिवर्तन लाने के जीनोम के भाग का डी एन ए मेथिलिकरण करने की सुविधा दे सकती हैं। विभिन्न होम्योपैथिक औषधियों के द्वारा लक्षित किए गए गुणसूत्रों और लक्षित गुणसूत्रों के द्वारा एन्कोड किए गए प्रोटीन के कार्यों की समझ होम्योपैथी औषधियों के चयन के लिए एक संपूरक दृष्टिकोण प्रदान करता है। इस समीक्षा में, उदाहरणार्थ, हम देखते हैं कि कैसे होम्योजेनोमिक अध्ययनों के परिणाम कैंसर से पीड़ित रोगियों में होम्योपैथिक उपचार के अक्सर प्रयोग की प्रयोज्यता का समर्थन करते हैं विशेष रूप से जीन टीपी 53 के नियमन के संबंध में। होम्योजेनोमिक अध्ययन के परिणाम पोटेंसी चयन और आदर्श खुराक पद्धति में भी सहायता प्रदान कर सकता है।

### La contribución de los estudios homeogenómicos y homeogenéticos en apoyo de la práctica homeopática

#### RESUMEN

Hace casi dos décadas, se postuló que los medicamentos homeopáticos podían ejercer sus efectos beneficiosos interactuando de algún modo en el mapa genético. A lo largo de los años, los resultados de muchos estudios homeogenómicos creíbles han confirmado este postulado. Los resultados de estos estudios han empezado a reconocer cuales de los aproximadamente 25.000 genes humanos estimados constituyen la diana de los medicamentos homeopáticos y cómo se reorganizan sus perfiles de expresión. Desde un punto de vista mecanicista, los estudios seminales homeogenomic han demostrado que los remedios homeopáticos también pueden facilitar las modificaciones epigenéticas como la metilación del ADN. Este es un descubrimiento importante ya que la metilación del ADN juega un papel importante en el control de la expresión de muchos genes. El conocimiento de los genes a los que se dirigen los medicamentos homeopáticos, en combinación con la información sobre la función de las proteínas codificadas por los genes diana, ofrece un enfoque complementario para la elección del medicamento homeopático. En esta revisión, como ejemplo, se muestra cómo los resultados de los estudios homeogenomic apoyan la aplicabilidad de los remedios homeopáticos utilizados con frecuencia en los pacientes que sufren de cáncer, en particular con respecto a la regulación positiva del gen TP53. Los resultados de los estudios homeogenómicos también contribuyen a la selección de la potencia y la pauta de dosificación óptima, comentada más abajo.