Database

on

Metallopharmaceuticals

Prepared for

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By

URDIP

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1. Introduction

Metals have played an important role in medicine for years, ever since humans have walked the planet. Many are essential in our diets in varying quantities, although people have only recently realized their significance. This could probably be attributed to our increased awareness of personal and families' health, and increased media involvement in our lives.

However at the other extreme, certain metals remain toxic in trace amounts, which can enter the body via a variety of routes and often cannot be excreted leading to metal toxicity. Until recently many people were unaware of the full extent of the risk of metal toxicity, for example in the use of lead piping in houses; the legacy of which continues to this very day.

Despite the dangers metals can pose to the human body, they are also used in the medical profession as invaluable diagnostic tools. These include radioactive and magnetic techniques using a variety of exotic elements to explore the inner structures of the human body without the need for invasive procedures.

Inorganic chemistry and the use of metals in therapeutic drugs have become increasingly important over the last couple of decades resulting in a variety of exciting and valuable drugs such as *cis*-platin for cancer. Research is underway to explore the use of other metals in fields such as diagnosis and treatment of cancer, arthritis, diabetes and cardiovascular diseases.

The unique properties of metal complexes tend to offer advantages in the discovery and development of new drugs. The metal complexes are amenable to combinatorial synthetic methods, and an immense diversity of structural scaffolds can be achieved. Metal centers are capable of organizing surrounding atoms to achieve pharmacophore geometries that are not readily achieved by other means. Additionally the effects of metals can be highly specific and can be modulated by recruiting cellular processes that recognize specific types of metal-macromolecule interactions. Metals can be useful probes of cellular functions. Understanding these interactions can lead the way towards rational design of metallopharmaceticals and implementation of new co-therapies.

2. Present Status of Metallopharmaceuticals

Recently, Metals in Medicine has been recognised internationally as an important area for research. There is evidenced by increased funding through a special National Institute of Health (NIH), USA program, the new Metals in Medicine Gordon Conferences and two European Union COST collaborative programmes.

The current literature also shows that metallopharmaceuticals is an area of growing interest as is evident through the clinical trials that are being conducted worldwide for the usage of metals in therapeutics. For e.g.; clinical trials for Silver biotics have been carried out for assessing its efficacy in a wide diversity of human problems, including malaria, upper respiratory tract infections, urinary tract infections, sinusitis infections, vaginal yeast infections, eye, nose and ear infections, cuts and fungal skin infections and even for sexually transmitted diseases like gonorrhea etc. proving it to be an antibiotic alternative at a convenient dosage.

Importance of Metal-based Drugs

Metals have been proven to have a number of applications in therapeutics and newer research avenues. Some of which are listed below:

Anti-Cancer Drugs

The most widely used drugs in chemotherapy (Pt drugs) are metal-based drugs and there are a large number of other metals that exhibit powerful anti-cancer effects. Titanium compound (titanocene dichloride) had been recognised as being active against certain breast and gastrointestinal carcinomas, although liver damage has been shown to be the dose-limiting side effect. Like titanium, gallium salts have been shown to have anti-cancer activity, probably delivered through transferrin. The gallium salts showa their synergistic effect with cis-platin in the treatment of lung cancer and urothelium carcinomas Similarly in ruthenium(III) the active mechanism involves transferrin delivery to tumor cells. Gold(I) complexes have also been shown to have anti-cancer activity, although through a different mechanism to cis-platin. There is also research into cytotoxic cobalt complexes, which could be pH-dependent cell-selective antitumor agents.

Anti-inflammatory Drugs

All anti-inflammatory drugs (including the new COX-II inhibitors) can have serious side effects and the costs of treating these side effects are even greater than the costs of the drugs themselves and lead to over 10,000 deaths per annum worldwide. Extensive research is being conducted into Cu and Zn anti-inflammatory drugs that have fewer side effects with similar or higher efficacy than the parent organic drugs commonly in use. Some such drugs are in the advanced stages of development and are expected to go to clinical trials soon.

Anti-diabetics

The safety, efficacy and mode of action of Cr and V anti-diabetic drugs are being investigated. Research is underway into the understanding of the metabolism of Cr dietary supplements, which constitute a billion dollar per annum industry, but pose a potential cancer risk to many who take such supplements. There is also active research going on in vanadium anti-diabetics, particularly in understanding their metabolism. These drugs hold considerable promise for both treating diabetes and its side effects. Research is also being performed on the effects of insulin on Cu metabolism, which may be linked to the fact that insulin does not treat the degenerative side effects of diabetes.

Anti-Microbials

Many metal complexes have powerful anti-microbial activities and are already in common day-to-day use such as silver bandages for treatment of burns, Zn antiseptic creams, bismuth drugs for the treatment of ulcers, and metal clusters as anti-HIV drugs. The potential for further development of metal-based drugs and treatments as anti-microbial agents are enormous and also of great importance with the evolution of drug-resistant bacteria and threats from a range of viral diseases. Research is being carried out in the development of such drugs, with anti-bacterial, anti-fungal and anti-viral activities, as well as specialists in the molecular biology of microbes, including targeting metal metabolic pathways and metalloenzymes in microbes for the development of new agents

Metal Deficiency Diseases

Metal deficiency diseases have long been known, and diets deficient in Ca, Cu, Zn and Fe are known to cause serious health problems. More recently, selenium deficiency is of increasing concern. The research into metal metabolism will provide new insights into the essential roles of metals in human health and the effective delivery of trace metals to treat deficiency diseases.

Metals in Degenerative Diseases

While many metals, such as Cu, Zn and Fe are essential for human health and protects human against many diseases, they are also implicated as being involved in many degenerative diseases, including atherosclerosis (heart disease and strokes), degenerative brain disorders, arthritis, cancers, etc. Normally, human metabolic processes tightly control the distributions and concentrations of such metals and the causes of these metal-imbalances, which may be an important factor in all degenerative diseases, are uncertain.

Biomineralisation

Biomineralisation processes are essential for human health in the formation of bones and teeth and in the storage of iron in ferritin. Malfunctions of these processes are responsible for serious birth deformities and other diseases. Hence, the genetic control of such processes needs to be better understood. In addition biomineralisation processes have essential roles in the lifecycle of serious diseases such as malaria, where the parasite causes the biomineralisation of heme groups that would otherwise be toxic to the invading parasite. There is growing evidence that most anti-malarials target this biomineralisation, hence a better understanding of the process will lead to better treatments for malaria.

New drug delivery systems

Metal-based drugs often have specific requirements for effective delivery systems, due to their higher chemical reactivities than most organic drugs. The fact that many drugs can undergo substitution and/or redox processes in formulations (or before they reach their targets), that special care needs to be taken in developing appropriate formulations, and characterisation of the stabilities of metal drugs in these formulations and drug delivery systems.

3. Database Creation

The objective of the of the project was to study the literature and patents on emerging field of Metallopharmaceuticalls and create an indexed and classified database on the basis of diseases and metals.

The focus was on research that bridges the areas of inorganic chemistry and medicine. This database brings together all the dispersed information for the development of successful metallopharmaceuticals and herbominerals.

A user-friendly database is designed to search by a metal name that can provide a list of all medical conditions where the metal is used for treatment with the complete metal profile covering details like modern metallo-complex medicines, various stages in preparation, medicinal properties, dosage, and in-vitro, in-vivo, clinical trials and toxicity studies of metals.

a. Data Collection

Short Listing of Literature Resources and Database to be searched. The literature was searched using online databases of peer-reviewed journals. The online resources and databases used were as follows:

For literature search

- Open databases like PubMed, Google Scholar etc.
- Well-known Publishers' websites like Elsevier, Wiley Inter science, American Chemical Society etc.
- Paid databases like SciFinder, Chemical Abstracts etc.

For Patent Search

- Open databases like USPTO, Esp@cenet
- Paid Databases like Delphion, Micropatent etc.

- Books - "Metallotherapetic Drugs and Metal based Diagnostic Agents" by Marcel Gielen and Edward R.T. Tiekink. Publisher-John Wiley and Sons, Ltd

Search terms used for data collection were as follows:

The literature was searched using the following broad search strategy. While creating search strategy maximum synonyms of the terms were used to collect relevant data.

"Metals in Medicine", " Metals and Pharmacy", "Metals and Drugs", Metallopharmaceuticals, "Inorganic Medicine", "Medicinal Inorganic", "Medicinal Coordination Chemistry", "Biomedical Inorganic Chemistry", "Elemental Medicine", "Metallodrugs". •

Review of the collected data was done. It was found that the maximum work on Metallopharamceuticals has been started after 1990. Hence scope of the database was limited to 1990 but not restricted.

Short-listing of Metals

A large ofnumber of results was retrieved which indicates that these metals are widely used. The list of metals selected for the database is shown below in Table 1.

Actinium	Iron	Ruthenium
Aluminium	Lanthanum	Samarium
Antimony	Lead	Scandium
Arsenic	Lithium	Silver
Astatine	Lutetium	Strontium
Bismuth	Manganese	Technetium
Chromium	Molybdate	Terbium
Cobalt	Nickel	Thallium
Copper	Niobium	Tin
Dysprosium	Palladium	Titanium
Erbium	Platinum	Tungsten
Gadolinium	Radium	Vanadium
Gallium	Rhenium	Yttrium
Gold	Rhodium	Zinc
Holmium	Rubidium	Zirconium
Indium		

Table 1. Metals included in the Database

In the next step, detailed literature and patent search was done for each metal by using following search terms

Literature

–“Metal Name” AND (Drug or Pharmaceuticals or Medicine or Therapeutics)

Patents

– ((Metal Name) <in> (title, abstract, claims) and (Drug or Pharmaceuticals or Medicine or therapeutics) <in> (title, abstract, claims))

b. Data Analysis: Includes Data Classification and Indexing

Data Classification

Using search strategy explained above data was collected from different resources and then it was classified into three categories

(i) Therapeutic Metallopharmaceuticals

(ii) Diagnostic Metallopharmaceuticals

(iii) Toxicity of Metals and Complexes

(i) Therapeutic Metallopharmaceuticals

These types of pharmaceuticals in the database are mainly classified on different types of activities against the diseases for which pharmacological, antibacterial and clinical studies are carried out. Some representative activities are listed below:

- Anticancer and antitumor activities e.g. metal based drugs used in chemotherapy: Ar, Cr, Se, Sn
- Antidiabetic activity ---- Cr, V
- Antibacterial, antifungal and antiviral activities
- DNA binding and intercalating activities
- Enzyme inhibition activity
- Chelators for treatment of metal intoxication
- Antidepressant activity
- Nuclear and radio activity

Apart from this metal-based drugs are also classified on the basis of “metal deficient diseases”, “degenerative diseases” and biomineralization.

(ii) Diagnostic Metallopharmaceuticals

Many metals are used in various diagnosis procedures. Such metals mainly include

- Diagnostic radiopharmaceuticals, e.g. metals used for radio labeling
- MRI contrast agents
- X-ray contrast agents
- Photo and radio sensitizers

(iii) Toxicity of the Metals and Complexes

Toxicity data of the metals and various complexes reported in literature are added in the database. The data includes in vivo and in vitro toxicity studies reported in the literature.

c. About Database

There are about 2,700 records in the database from published literature as well as patents. The database gives bibliographic details and abstract of the publication (Details in next section)

The database contains 690 patents from all over the world. The criterion for including patent was one patent per Patent family. The patents having only bibliographic details and without any abstract are not included in the database.

The literature records in the database include the data on clinical trial on human as well as animals. The data on the mechanism of action or activity of the complex is also included. For e.g. The anti-diabetic complex/compound can be insulin mimicking (Vanadium) or can control cellular glucose uptake (Chromium).

The toxicology data in the database is from the literature reporting toxicity studies on humans and animals. The data includes animal used in the study, type of toxicity, LD_{50} or Maximum dose given in the study.

The database also contains metal and its compounds used in various Diagnosis techniques of the modern medicine like Boron neutron capture therapy, Imaging Agent, MRI contrast agent, Radiotracer etc. There are about 500 records in the database on these agents.

d. Software Development

Software for the data entry and retrieval was developed In house at URDIP. It is a CD based desktop application using Visual Basic as a front end and MS-Access as a backend. The database structure includes bibliographic details with abstract. The database was slightly modified for literature and patent bibliography as per requirement. The detailed database structure is as given below.

DATABASE STRUCTURE – The database structure includes the following fields.
LITERATURE:

- Title of the article,
- Authors,
- Name of the journal,
- Vol No (issue No), Page No,
- Name of the metal,
- Name of the Complex name,
- Diseases Name
- Mechanism or mode of action in which metal complex acts in the body,
- Abstract of the article
- Keywords.

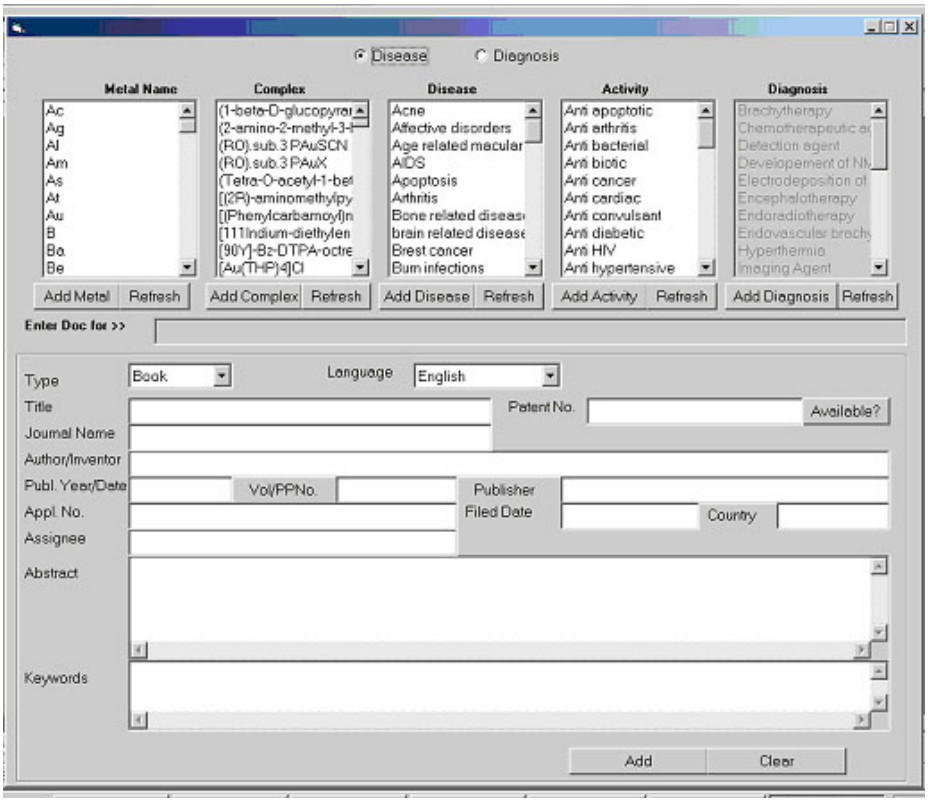
Patent - Database structure was designed for patents, which includes following fields:

- Title of the Patent,
- Patent No.
- Assignee,
- Inventors,
- Date of Grant,
- Date of Application,
- Assignee Country,
- Language,
- Name of the metal,
- Complex Name,
- Name of the Diseases conditions

- Mechanism or mode of action
- Abstract of the patent
- Keywords.

Data Entry format

A separate Client-Server based DB entry tool was developed so that any number of knowledge workers can work simultaneously to prepare database. Easy navigation, view and search facilities were developed for verification



The data retrieval part of the database is very important as is used by user and not the developer. This database retrieval is done by using the browsing the database option or by using search engine option with simple or advance search facility. The search engine is developed in house at URDIP.

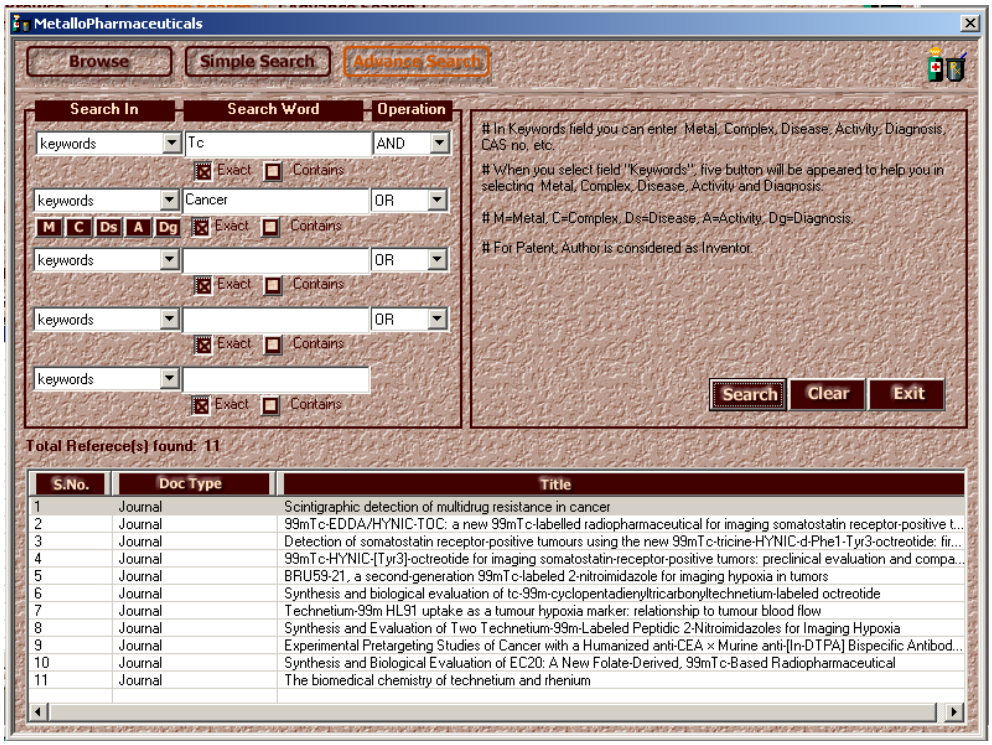
Browse/Simple Search/Advanced Search:

This database is very user friendly and provides the user with three choices depending on the user's requirements.

- User can Navigate the database by browse option
- User can enter queries to Simple search.
- Using Boolean operators for Advanced search

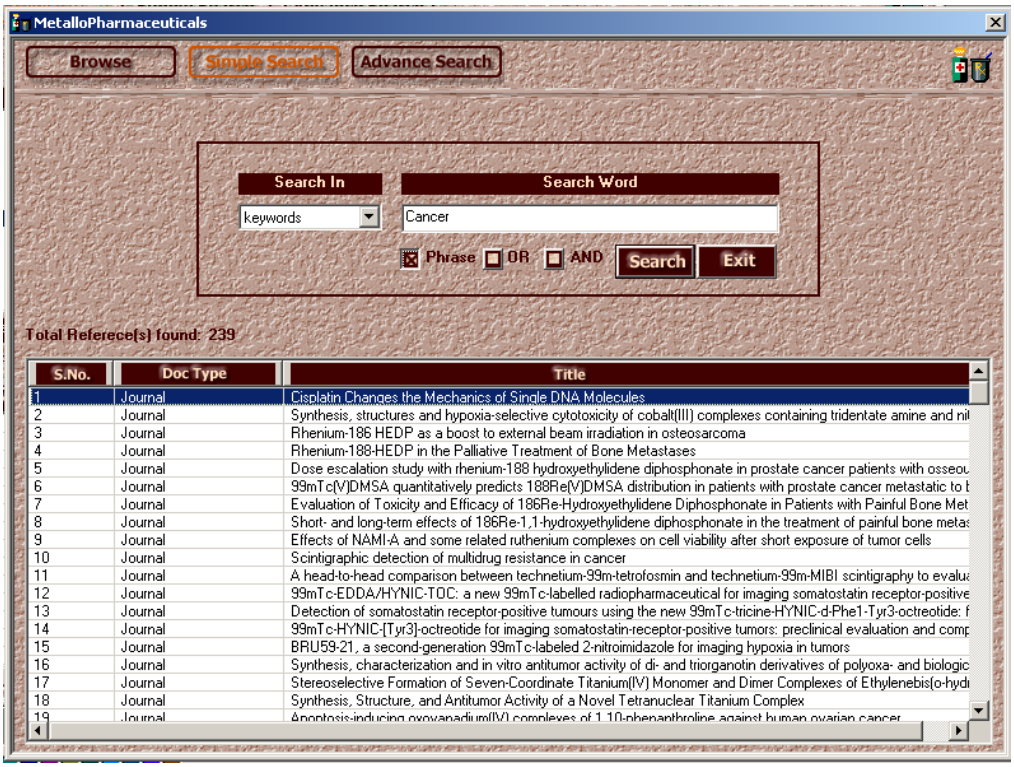
Advanced Search

In this search facility, user can specify the search terms by using Boolean operators like AND, OR and NOT options to get the precise results. These operators can be used for combining various data fields like metal name, Disease Name or any related word under the field Keywords. Pressing the corresponding button and selecting it for the search can retrieve the list of Metals (M), Diseases (Ds), Complexes (C), Diganosis (Dg), Activity (A) in the database. The sample screen showing advance search is as shown in the figure 1.



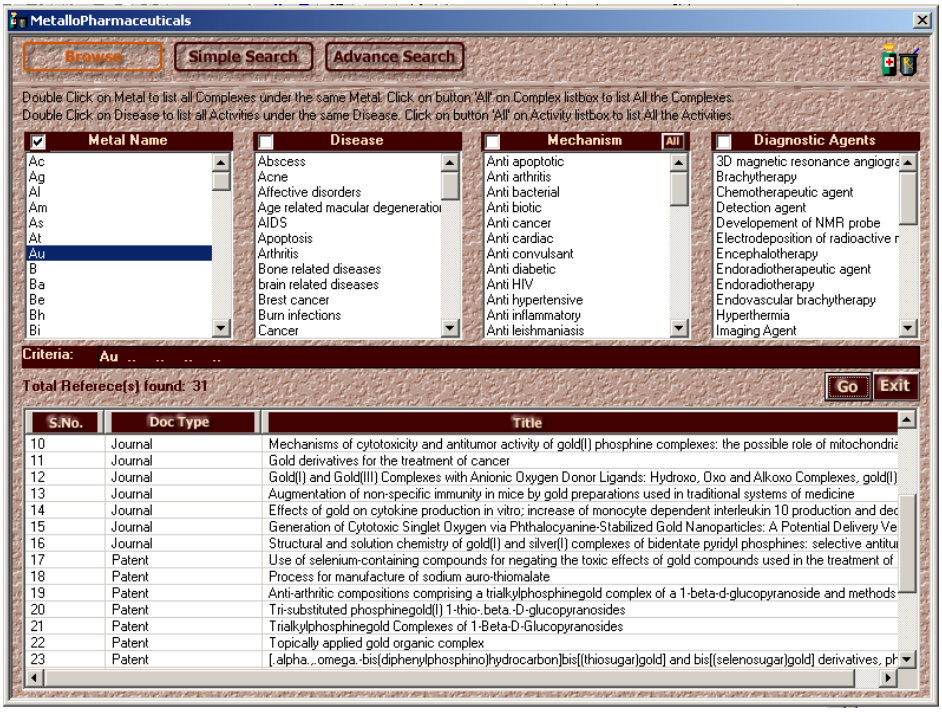
Simple Search

In this option, user can select any one field at a time to search the database. User has the option of using AND, OR restricted to the single field to get the precise results. The sample screen showing simple search is as shown in the figure 2.



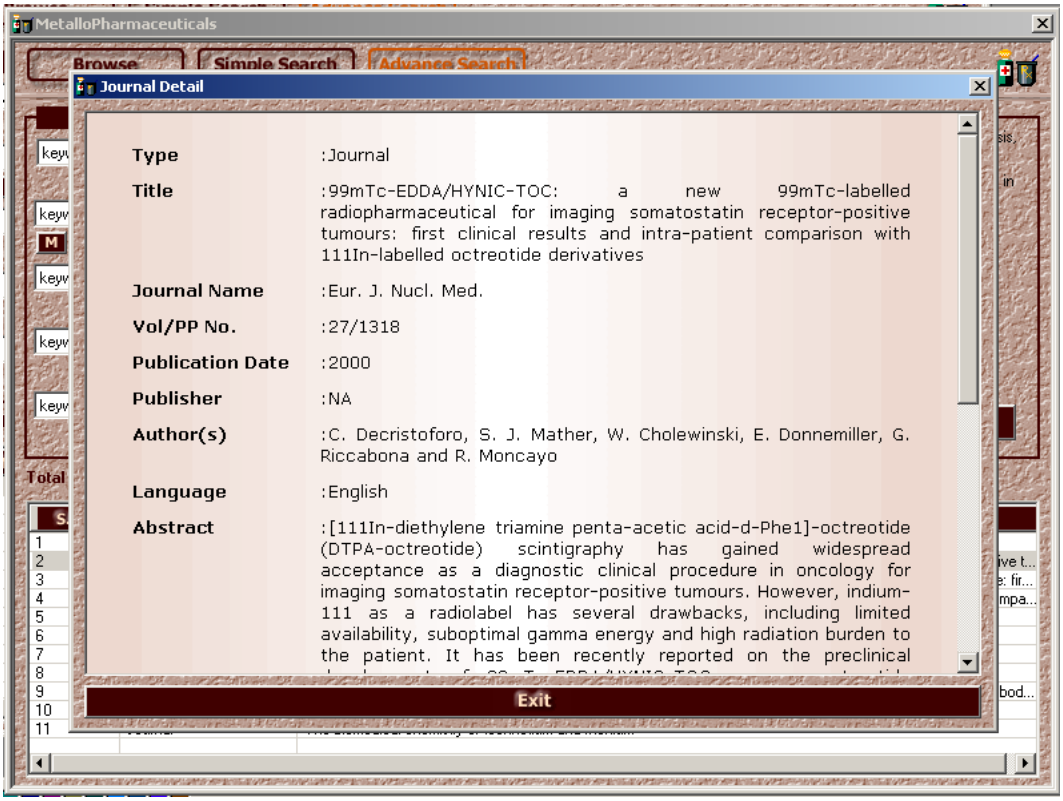
Browse Data

The user can retrieve the data by using this option. To assist the user list of all the fields like Metal, Disease, Mechanism of Action and Diagnostic Agents would be displayed on the screen. The user has to select the required word and double click it to get the result. As seen in figure 3 below, the user would be able to see the browse screen.



In all the three search options above, the resultant records can be seen in a table giving Sr. No, Doc Type (Patent or Journal) and title of the publications. Once user selects the particular record and double clicks on it, the detailed record would be displayed with bibliographic details and abstract. The sample record is as shown in figure 4.

Sample record



Future Uses of the Database

The development of a database that can integrate together all the information about metals that have been reported to be useful for the treatment of a particular disease along with their possible mechanisms of action at the molecular level, the methods of preparation rendering them non-toxic, the accuracy of dosage to strike a balance between therapeutic effect and toxicity, can be very useful in a variety of ways in modern drug research. Some examples of this are:

1. Design of effective delivery systems of metallopharmaceuticals into target cells and to specific intracellular sites
2. Ligand design to optimize desired metal complex properties (thermodynamic and kinetic stability, hydrolytic stability, catalytic activity, molecular weight, charge, lipophilicity, water solubility, targeting functionalization, and ligand metabolism
3. Development of better in vitro screens and animal models to provide better prediction of human efficacy and toxicity

Summary

This is a first attempt of its kind to build a database of metals in medicine that brings all the worldwide information in the area of metallotherapeutics at the fingertip of a researcher.

The unique properties of metal complexes tend to offer advantages in the discovery and development of new drugs. The metal complexes are amenable to combinatorial synthetic methods, and an immense diversity of structural scaffolds can be achieved. Metal centres are capable of organizing surrounding atoms to achieve pharmacophore geometries that are not readily achieved by other means. Additionally the effects of metals can be highly specific and can be modulated by recruiting cellular processes that recognize specific types of metal-macromolecule interactions. Metals can be useful probes of cellular function. Understanding these interactions can lead the way toward rational design of metallopharmaceticals and implementation of new co-therapies.

Metal-based agents can modify both DNA and RNA with a high degree of regiochemical, sequential, and conformational specificity. Simply targeting DNA is no longer a sufficient rational for testing a compound (whether organic or inorganic). Cell selectivity in mRNA expression makes it an attractive target. The metal complex-based selective enzyme inhibition is an under explored area. Metals may be useful in active site recognition and in bifunctional agents as secondary contacts to increase inhibitor affinity.

Metal complexes can be potent and highly selective ligands of cell surface receptors. The influences of metals on the host of other known cellular targets remain largely unexplored, except in the context of metal toxicity. Studies of toxicity mechanisms may provide insights into potential therapeutic approaches. Essential metals are being developed as both drugs and dietary supplements. Several metals (e.g., vanadium and chromium) appear to have significant effects on complex metabolic diseases (e.g., diabetes). The mechanisms of these effects are still unclear. Metal complexes have been developed that are stable, yet have superoxide dismutase, catalase, and peroxidase catalytic activities. Such complexes may be useful in a host of oxygen radical-mediated disease processes. Metal complexes have shown potent anti-viral and anti-cancer activities in a variety of screens. Herbal research also tends to involve the usage of complexes between compounds isolated from herbs and metals for herbo-mineral formulations.

Thus metals can have a significant market (and health benefit) impact, and significant growth potential. New agents are likely to find unique market niches due to unique mechanisms of action or pharmacokinetic properties that complement other therapeutics