INTERNATIONAL JOURNAL OF PHARMACEUTICAL RESEARCH AND DEVELOPMENT (IJPRD)
Platform for Pharmaceutical Researches & Innovative Ideas
www.ijprd.com

FORMULATION OF SUSTAINED RELEASE TABLET OF ANTI OBESITY DRUG GARCINIA CAMBOGIA

Atul Sethi[1*],
Dindayal Patidar[1], Neeraj Patidar[1], Deepak Shrivastava[1], Nadeem Farooqui[1]

[1]Indore Institute of Pharmacy (IIP) Indore Rau-Pithampur Road Indore (M.P.)

ABSTRACT

Obesity is a major problem in the effluent socities of developing and developed world and the Health Risks associated with the obesity are Diabetes mellitus, Heart disease, High b.p.,etc.

WHO report –Globally with more than 1 billion adults overweight - at least 300 million of them clinically obese. Now a days herbal drug are used because of its lesser side effects as compared to synthetic drugs. The purpose of this present work is to formulate an oral sustained release matrix tablet of Garcinia cambogia in an attempt to design a dosage form that manifests desirable release profile. The Garcinia fruit is a rich source of hydroxycitric acid (HCA), the active agent that aids in weight loss by inhibiting fat production and suppressing appetite. Garcinia cambogia extract is quickly becoming a popular ingredient in many weight loss supplements.

Key words: sustained release tablet, antiobesity drugs, herbal medicines, Garcinia cambogia, hydroxycitric acid (HCA).

Correspondence to Author

Atul Sethi

B.Pharmacy (VIII Sem.) Indore Institute Of Pharmacy(IIP) Indore
Address: 60, Somani Nagar, Airport road, Indore (M.P.)

Email: atulsethi007@yahoo.com

INTRODUCTION

Obesity is a medical condition in which excess body fat has accumulated to the extent that it may have an adverse effect on health, leading to reduced life expectancy and/or increased health problems.

Obesity is one of the leading preventable causes of death worldwide. November 26th, 2010 is dedicated as Anti-Obesity Day in India. A herbal drug Garcinia cambogia has been used as an anti obesity drugs and till today it has been marketed in capsule dosage forms. We are now giving emphasis on formulating its sustained release dosage form.

Garcinia cambogia [4] : The fruit of Garcinia cambogia has been traditionally used in food preparation and cooking. In Ayurveda,it is said that sour flavors such as those from Garcinia activate digestion. Garcinia is considered to make foods more filling and satisfying and has been used routinely for many centuries with no toxicity.

Garcinia and its active ingredient, HCA (hydroxycitric acid) have been extensively studied for over thirty years and found to be effective in inhibiting lipogenesis, suppressing appetite, and encouraging weight-loss in humans.

Garcinia cambogia is a diminutive purple fruit native to India and Southeast Asia. It is used as a weight loss aid, but the evidence is inconclusive. The rind is rich in hydroxycitric acid (HCA) and has

been used for centuries throughout Southeast Asia as a food preservative, flavoring agent and carminative (induces expulsion of gas from stomach or intestines). According to Indian folk tradition, Garcinia cambogia is used for rheumatism and bowel complaints. Neither acute nor chronic toxicity is reported with regular consumption of garcinia products as either food or tonics. These products have been used routinely in the coastal areas of South Asia for centuries and they continue to be consumed in large amounts. There is preliminary evidence for the use of garcinia in exercise performance and weight loss.

Pharmacognostic Study [5,6]

Botanical Name: Garcinia cambogia

Family: Guttiferae

Plant Parts Used: Fruit rind

Common/Trade Names: Vilati – Amli

Sanskrit and Hindi Names:[7] Vrikshamla

Other Common Names: Brindle berry, brindall berry, garcinia, malabar tamarind, gambooge, gorikapuli, uppagi, garcinia kola, mangosteen oil tree.

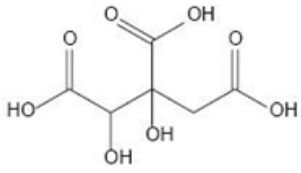
Habitat: India and South East Asia.

Chemical Constituents:[8] The plant contains various chemical constituents such as Xanthones, Benzophenones,Garcinol and plant acids like (-) Hydroxy Citric Acid, Maleic acid, Citric acid.

HCA is naturally occurring fruit acid found in the outer layer covering of the fruits of Garcinia cambogia.

HCA is highly unstable and therefore extracted as a salt of preferably as calcium or potassium.

Hydroxycitric acid



(-)-Hydroxycitric acid

MW: 208.12 g/mol

MF: $C_6H_8O_8$

Dosing:

Adults (over 18 years old)

Dosing evidence is conflicting, and there is no proven effective dose for garcinia. There is sufficient available scientific evidence suggesting that intake of hydroxycitric acid at levels up to 2,800 milligrams per day is safe for human consumption.

Garcinia has been well tolerated for up to 12 weeks in available human trials.

For exercise performance, 250 milligrams of hydroxycitric acid capsules administered for five days may be beneficial.

Interactions

Interactions with Drugs:

Garcinia may lower blood sugar levels. Caution is advised when using medications that may also lower blood sugar.

Patients taking drugs for diabetes by mouth or insulin should be monitored closely by a qualified healthcare professional, including a pharmacist. Medication adjustments may be necessary.

Taking hydroxycitric acid with statin medications, such as atorvastatin calcium (Lipitor), may increase the risk of rhabdomyolysis (disease involving the degeneration of skeletal muscle).

An incidence of rhabdomyolysis was reported in a case report of a patient taking a weight-loss herbal medicine that contained 50% hydroxycitric acid.

Interactions with Herbs & Dietary Supplements:

Garcinia may lower blood sugar levels. Caution is advised when using herbs or supplements that may also lower blood sugar.

Blood glucose levels may require monitoring, and doses may need adjustment.

The combination of calcium/potassium-bound hydroxycitric acid complex with niacin-bound chromium or Gymnema sylvestre may increase the effects on weight loss.

Consult with a qualified healthcare professional, including a pharmacist, before combining therapies.

Pharmacological Action of Garcinia cambogia. [9, 10]

Normally the body converts carbohydrates (glucose,fructose,galactose) taken by meal into energy(ATP) and the excess carbohydrates that cannot be used immediately for energy convert

into glycogen. Glycogen is the storage form of carbohydrates, deposited in muscles and the liver.
When the glycogen stores are reasonably full, additional carbohydrates are then converted into excess of extramitochondrial Acetyl CoA required for fatty acid synthesis using ATP Citrate lyase enzyme.

citrate + ATP + CoA + H_2O--->oxaloacetate + Acetyl-CoA + ADP + Pi.

(-)-Hydroxycitric acid [(-)-HCA] is the principal acid of fruit rinds of Garcinia cambogia
(-)-HCA was shown to be a potent inhibitor of ATP citrate lyase. The inhibition of this reaction limits the availability of acetyl-CoA units required for fatty acid synthesis and lipogenesis during a lipogenic diet, that is, a diet high in carbohydrates.
This added glycogen load in the liver stimulates a longer lasting neuro-signal from the liver to the brain, indicating satiety (satisfaction), thus helping to suppress appetite longer.
(-)-HCA as weight-controlling agent.
Therapeutic Dosages: Supplements are available in various forms including tablets, capsules, powders, extracts and even snack bars. Garcinia cambogia medications are usually standardised to contain fixed percentage of HCA.
The usual dosage for garcinia is 300 to 500mg tablets three times daily taken half an hour before meals with water.
Sustained Release Dosage Forms (SRDF's): [11-17]
Sustained release dosage forms are designed to release a drug at a predetermined rate by maintaining a constant drug level for a specific period of time with minimum side effects.
SRDF's describes the slow release of a drug substance from a dosage form to maintain therapeutic response for extended period (8-12hrs) of time.
Time depends on the dosage form. In oral form it is in hours, and in parenteral's it is in days and months.
Ex: Aspirin SR.
Aim: The main AIM of preparing sustained release dosage formulations (SRDF's) was intended to modify and improve the drug performance by:

* Increasing the duration of drug action. * Decreasing the frequency of dosing.
* Decreasing the required dose employed. * Providing uniform drug delivery.
Concepts: The Goal of SRDF's is to obtain Zero order release from the dosage form. Zero order release is a release which is independent of the amount of drug present in the dosage form.
Usually SRDF's do not follow zero order release but they try to mimic zero order release by releasing the drug in a slow first order fashion.
Pharmacological action is seen as long as the drug is in therapeutic range, problems occur when drug concentration is above/below therapeutic range.
Factors to Be Considered While Formulating A SRDF's:
Drug Properties: Stability, solubility, partition coefficient and protein binding are to be considered.
Route of Drug Delivery: Area of the body where drugs are applied or administered play a vital role.
Target Sites: To minimize side effects, its desired to maximize the fraction of dose applied.
Acute Or Chronic Dosing: Cure, Control and length of drug therapy must be considered.
The Disease: Pathological conditions play a significant role.
The Patient: Ambulatory/ bedridden, young or old, etc., must be considered.
Physicochemical Properties Of Drug: Aqueous Solubility & pka, Partition Coefficient, Drug Stability, Protein Binding, Molecular Size & Diffusivity, Dose Size.
Techniques for Preparing SR Formulations:
Based On Drug Modification
Complex Formation, Drug-Adsorbate Preparation, Pro Drug Synthesis, Ion Exchange Resins.
Based On Dosage Form Modification
Microencapsulation, Barrier coating, Matrix embedding
Based On Drug Modification
Complex formation: The rate of dissolution of solid complex in biological fluids and rate of dissociation of complex in the solution are considered and they depend upon pH and composition of gastric and intestinal fluids.

Drug-adsorbate preparation: In this product is insoluble. Drug availability is determined by rate of disabsorption.

Pro drug synthesis: They are inactive and need enzymatic hydrolysis for regeneration. Solubility, absorption rate of prodrug must be lower than parent drug.

Ion exchange resins: They are water insoluble, cross linked polymers containing salt forming groups. The drug is bound to the resin by using chromatographic column or by prolonged contact.

Drug release from this complex depends on pH & property of resin. Drug that is attached to the resin is released by exchanging with the ions present in the GIT.

Resin+ -Drug- +X- ----------→Resin+- X- + Drug-

Example: Biphetamine.

Based On Dosage Form Modification:

Microencapsulation: It's a process in which tiny particles are surrounded by uniform coating (microcapsule) or held in a matrix of polymer (microsphere) Spray drying is used which involves rapid evaporation of the solvent from the drug surface.

Barrier coating: In this one quarter of the granules are in non sustained form for sudden drug release, remaining part is coated for sustained release. Both these granules are filled in hard gelatin capsule or compressed in a tablet, and the release mechanism is by diffusion.

Coating material used are fats, waxes.

Matrix embedding: Drug is dispersed in a matrix of retardant material which may be encapsulated or compressed in a tablet.

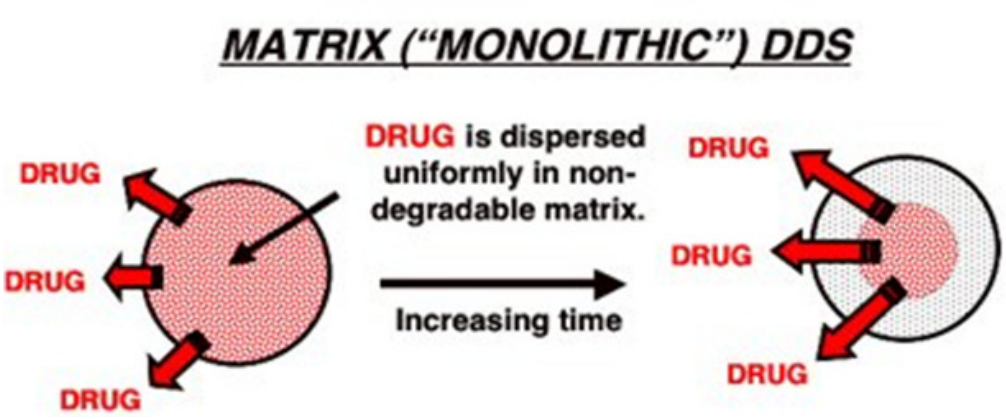


Fig 1 Matrix embedded drug release pattern

Evaluation:

i) Micromeritic properties:-

a) Angle of repose: The angle of repose of powder was determined by the funnel method. The accurately weighed powder was taken in a funnel. The height (h) of the funnel was adjusted in such a way that the tip of the funnel just touches the apex of the heap of the powder. The powder was allowed to flow through funnel freely onto the surface.

The diameter of the powder cone was measured and angle of repose was calculated using the following equation.

$$\tan \Theta = h/r$$

Therefore, $\Theta = \tan^{-} h/r$

Where, Θ = angle of repose,

h = height of the pile,

r = radius of the pile base

Bulk density: Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. Powder from each formulation, previously lightly shaken to break any agglomerates formed was introduced into a 10 ml measuring cylinder.

After the initial volume was observed, the cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5 cm at 2 sec intervals.

The tapping was continued until no further change in volume was noted. Bulk density is calculated by using formula:

Bulk density $= \frac{\text{Weight of the powder}}{\text{Volume of the powder}}$

Tapped density:

$$\text{Tapped density} = \frac{\text{Weight of the powder}}{\text{Tapped volume of the powder}}$$

Carr's index: It helps in measuring the force required to break the friction between the particles and the hopper. It is expressed in % and given by:

Carr's index (%) = [(TBD - LBD) x 100]/TBD

Where,
LBD = weight of the powder/volume of the packing
TBD = weight of the powder/tapped volume of the Packing

Physicochemical parameters:-

Tablet hardness: The resistance of tablet for shipping or breakage, under conditions of storage, transportation and handling, before usage, depends on its hardness. The hardness of tablet of each formulation was measured by using Pfizer hardness tester.

Tablet thickness: Thickness of tablets was important for uniformity of tablet size. Thickness was measured by using screw gauze on 3 randomly selected samples.

Friability: Friability is the measure of tablet strength. Roche Friabilator was used for testing the friability using the following procedure. Twenty tablets were weighed accurately and placed in the plastic chamber that revolves at 25 rpm for 4 mins dropping the tablets through a distance of six inches with each revolution. After 100 revolutions the tablets were reweighed and the percentage loss in tablet weight was determined.

$$\% \text{ loss} = \frac{\text{Initial wt. of tablets - Final wt. of tablets}}{\text{Initial wt. of tablets}} \times 100$$

Weight variation: Twenty tablets were weighed individually and the average weight was determined. Then percentage deviation from the average weight was calculated.

According to IP standards, not more than two of the individual weight deviates from the average weight by more than the percentage shown in the (Table 7) and none deviates by more than twice that percentage.

Uniformity of drug content: Ten tablets were weighed and average weight is calculated. All tablets were crushed and powder equivalent to 8 mg drug was dissolved in 8 ml of 0.1N NaOH and the volume was made up to 100 ml with pH 6.8 phosphate buffer. The solution was shaken for 1 h and kept for 24 h. From the stock solution, 1 ml solution was taken in 10 ml volumetric flask and the volume was made with pH 6.8 phosphate buffers.

Solution was filtered and absorbance was measured spectrophotometrically at 379 nm against pH 6.8 phosphate buffer as a blank. Amount of drug present in one tablet was calculated.

Dissolution studies: The release rate of sustained matrix tablets were determined using USP dissolution testing apparatus II (paddle type) at 50 rpm. The dissolution test was performed using 750 ml of 0.1 N HCl (pH 1.2) for 2 h at 37 ± 0.5 °C and then 250 ml of 0.2 M tri sodium phosphate ($Na_3PO_4.12H_2O$) was added and pH is adjusted to 6.8 as described in the USP 26/NF monograph.

Dissolution test was carried out for a period of 12 h using 0.1N HCl (pH 1.2) for first 2 h and then the pH is adjusted to 6.8 for the rest of the period. The temperature of the dissolution medium is maintained at 37±0.5°C. 10 ml of the sample was withdrawn at regular intervals and replaced with the same volume pre-warmed with fresh dissolution medium. After filtration, the amount of drug release was determined from the standard calibration curve of pure drug.

Stability Studies For the Most satisfactory Formulation of Sustained Release Matrix Tablets:

Stability testing of drug products begins as a part of drug discovery and ends with the demise of the compound or commercial product. To assess the drug and formulation stability, stability studies were done according to ICH guidelines. The stability studies were carried out of the most satisfactory formulation as per ICH guidelines.

The most satisfactory formulation sealed in aluminum packaging and kept in humidity chamber maintained at 30 ± 2 °C / 65 ± 5 % RH and 40 ± 2 °C / 75 ± 5 % RH for two months.

At the end of studies, samples were analyzed for the drug content, *in vitro* dissolution, sustained behavior and other physicochemical parameters.

EXPERIMENTAL WORK

Methodology:

Preformulation Parameters:[18]

Polymers: The polymers used in the preparation of hydrophilic matrices are Hydroxyethylcellulose, Hydroxypropylmethylcellulose (HPMC) 25, 100, 4000 and 15000 cps, Sodium carboxymethylcellulose and Methylcellulose 400 and 4000 cps.

Binder: Poly vinyl pyrrolidone (PVP): PVP also commonly called Polyvidone or Povidone, is a water soluble polymer made from the monomer *N*-vinylpyrrolidone.

It is used as a binder in many pharmaceutical tablets.

Povidone is used as binder (at a concentration of 0.5% w/w to 5 % w/w) in tablets. It also acts as a solubilizer and enhances the dissolution of poorly soluble drugs from solid dosage forms. The molecular adduct formation of povidone may be used to advantage in slow release solid dosage forms.

Lubricant: Magnesium stearate, also called octadecanoic acid, magnesium salt, is a white substance which is solid at room temperature. It has the chemical formula $Mg(C_{18}H_{35}O_2)_2$. It is a salt containing two equivalents of stearate (the anion of stearic acid) and one magnesium cation (Mg^{2+}). Magnesium stearate melts at about 88 °C, is not soluble in water, and is generally considered safe for human consumption at levels below 2500 mg/kg per day. It has lubricating properties, preventing ingredients from sticking to manufacturing equipment during the compression of chemical powders into solid tablets; magnesium stearate is the most commonly used lubricant for tablets.

Glidant: Aerosil**:** Aerosil is a registered trademark for fumed silica product.

It is a glidant that is added to a powder to improve its flowability.

Requirements:

Drug: Garcinia cambogia extract.

Chemicals: Ethanol, Chlorofom, HCL, Sulphuric acid, Diethyl ether, Carbon tetrachloride, Isopropyl Alcohol HPMC, PVP, Talc, Mg.Sterate, Lactose monohydrate, sucrose, dextrose, m.c.c, starch, etc.

Apparatus: Tablet punching machine, UV Spectrophotometer, Dissolution apparatus, Friabilator, stability chamber, etc.

Solubility:

Water:	Slightly soluble
Ethanol:	Insoluble
Methanol:	Insoluble
Chloroform:	Precipitate
Sulfuric acid:	Soluble
Hydrochloric Acid:	Soluble
Carbon Tetrachloride:	Precipitate
Isopropyl Alcohol:	Insoluble
Diethyl Ether:	Precipitate.

Absorbance:

2 µg/ml in 0.1N HCl was found to be 206 nm and absorbance was found to be 0.46

Table 1: Model HPMC Formulations Used in This Study

Ingredients	Concentration (%w/w)
Garcinia extract	77.25
HPMC	20.00
PVP	5.00
Fumed silica	0.50
Magnesium stearate	0.25
Colour,flavor,preservative, q.s. granulating agent	

Method of Preparation:

The Sustained Release tablets were prepared by wet granulation technique.

Weighed amounts of drug, diluent, HPMC, Preservative were taken into a bowl by passing through a 40 mesh screen and mixed manually for 5 min.

Then the blend was granulated using water as the granulating agent. The mass was dried in a hot air oven at 50°C and sieved through a 30 mesh screen. Magnesium stearate, fumed silica was then added to the dried, sieved granules and mixed for about 5 min in a poly-bag. The produced mixture was compressed into tablet.

CONCLUSION

Obesity is a major problem in the effluent socities of developing and developed world and the Health Risks associated with the obesity are Type 2 diabetes, Heart disease, Stroke High blood pressure,High blood cholesterol, etc. To get rid of these diseases it is necessary to avert obesity.

It is proposed that herbal drugs especially Garcinia cambogia are more beneficial in treatment of obesity because of its fewer side effects and to prevent diseases like diabetes mellitus, Heart disease, Stroke, High blood pressure before their occurrence.

Future Prospects

This drug (Garcinia cambogia) is very effective to overcome obesity or atherosclerosis which helps to reduce out the chances of stroke, shock, congestive heart failure, hypertension, kidney failure, diabetes which may occur due to excessive obesity.

This drug (Garcinia cambogia) is abundantly available in China.Capsule dosage form is available in market all over the world, till date they don't get success in other dosage forms like parenteral or oral sustained release tablet.

Now Indian pharmaceutical companies are working on oral sustained release tablet with full of enthusiasam to put that drug in the category of anti hyperlipidemic drug which is very advantageous as compared to conventional synthetic anti hyperlipidemic drug.

ACKNOWLDGEMENT

Authors are grateful to the Indore Institute of Pharmacy, Indore for providing the necessary facilities for undergoing this work.

We are heartly thankful to Dr. Yusuf Ali Jaliwala (Principal) and Prof. Umesh Parikh for their kind support and guidance.

We are thankful to all the faculty members, my classmates and all staff members for their direct and indirect support.

Special thanks to Sethi Rasayan Shala, Indore for providing the Garcinia extract.

REFERENCES

1. Parveen Kumari; "HERBAL FIGHT FOR OBESITY : A REVIEW" IJPRD, 2011; Vol 3(4): June 2011 (193 - 201)
2. Barness LA, Opitz JM, Gilbert-Barness E (December 2007). "Obesity: genetic, molecular, and environmental aspects". Am. J. Med. Genet. A 143A (24): 3016–34. doi:10.1002/ajmg.a.32035. PMID 18000969
3. Ness-Abramof R, Apovian CM (February 2006). "Diet modification for treatment and prevention of obesity". Endocrine 29 (1): 5–9. doi:10.1385/ENDO:29:1:135. PMID 16622287
4. Dallas Clouatre & Michael Rosenbaum. "The Diet and health benefits of HCA", Keats Publishing Inc. New York. 1990.
5. Shara, M., Ohia, S.E., Schmidt, R.E., Yasmin, T., Zardetto-Smith, A., Kincaid, A., Bagchi, M., Chatterjee, A., Bagchi, D. & Stohs, S.J. (2004) Physico-chemical properties of a novel (-)-hydroxycitric acid extract and its effect on body weight, selected organ weights, hepatic lipid peroxidation and DNA fragmentation, hematology and clinical chemistry, and histopathological changes over a period of 90 days. Molec. Cell Biochem., 260(1-2),171-186
6. Publications & Information Directorate, Council of Scientific & Industrial Research (1986). G. cambogia Desr. The Useful Plants of

India. (New Delhi: Publications & Information Directorate, 1986) 229.
7. Soni, M.G., Burdock, G.A., Preuss, H.G., Stohs, S.J., Ohia, S.E. & Bagchi, D. (2004) Safety assessment of (-)-hydroxycitric acid and Super CitriMax, a novel calcium/potassium salt. Food Chem.Toxicol., 42(9), 1513-1529
8. Heymsfield SB, Allison DB, Vasselli JR, Pietrobelli A, Greenfield D, Nunez C; Garcinia cambogia (hydroxycitric acid) as a potential antiobesity agent: a randomized controlled trial. PMID: 9820262
9. Steven B. Heymsfield, MD; David B. Allison, PhD; Joseph R. Vasselli, PhD;Angelo Pietrobelli, MD; Debra Greenfield, MS, RD; Christopher Nunez, Med; "Garcinia cambogia (Hydroxycitric Acid) as a Potential Antiobesity Agent" From the Department of Medicine, Obesity Research Center, St Luke's–Roosevelt Hospital, Columbia University College of Physicians and Surgeons, New York
10. http://ukpmc.ac.uk/abstract/MED/9820262/reload=0;jsessionid=DAE25B774B485FAA7C6504DFDFDF92E4
11. Text book of Sustained release dosage form by Y.S.Robinson, Decker Series
12. Controlled release dosage form by Y.W.Chien.
13. Ansel's Pharmaceutical Dosage forms and Drug delivery Systems.
14. Tutorial Pharmacy by Cooper and Gunns.
15. Remington's Pharmaceutical Sciences
16. Text book of Pharmaceutics by Bentley and Drivers.
17. Text book of Pharmaceutical Sciences by Aulton
18. http://www.ijddr.in International Journal of Drug Development & Research| Jan-March 2011 | Vol. 3 | Issue 1 | ISSN 0975-9344 |

Websites:
http://garcinia-cambogia.101herbs.com/
http://www.medicalnewstoday.com/info/obesity/
http://www.disabled-world.com/calculators-charts/whr-calculator.php
http://www.motherherbs.com/garcinia-cambogia.html
http://www.ayurvediccure.com/garcinia-cambogia.htm
http://www.streetdirectory.com/travel_guide/47311/lose_weight/garcinia_cambogia___a_natural_weight_loss_supplement_ingredient.html
http://www.wisegeek.com/what-is-garcinia-cambogia.htm
http://www.livestrong.com/article/404681-guggul-and-obesity.

*****