DISCUSSION

The Juvenile Diabetes refers to inability of the body to cope up with the maintenance of equilibrium of glucose in young individuals. The body is unable to utilize the glucose for its basic requirements. Due to lack of proper secretion of endogenous insulin from the destructed endocrine pancreatic cells. This ailment gets much attention especially in the early childhood diabetics. One of the main causes for such clinical manifestation is due to the autoimmune response where a numbers of autoimmune antibodies are involved in the destruction of the islet cells of pancreatic tissue and the patient depends on exogenous insulin to overcome from the prevailing situation due to associated underlying pathological process. Both type I and type II Diabetes Mellitus (DM) cause much financial burden on the country through direct and indirect medical expenditures, which costs millions of rupees every year. The need of the hour is an intense alternate and medical research to tackle this increasing disease incidence among young generation\textsuperscript{38}.

The children who develop the diabetes are showing substantial evidence of decrease in the IQ of the children who are diabetic since the early childhood. Such impact, have been assessed through the experimental parameters like nonverbal intelligence, verbal intelligence, information processing, visio-spatial ability, attention behavior, memory retention etc. The word Early Onset of Diabetes (EOD) refers to the recognition of the diabetic syndrome in the children below 7 years of age, or generally it is the age group between the 4-7 years. The recognition of volumetric changes in the patient’s brain associated with the EOD where the brain atrophy was seen, is an important detrimental in the early diabetic brain changes\textsuperscript{37}.  

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The diabetes treatment gets its greater concern especially during its early childhood manifestation, the primary aim of an alternate therapy is not only just to combat the excess blood glucose levels, but in addition it targets the protection of brain from excess of deranged glucose induced metabolic changes, which are likely to interfere with the ongoing pathophysiological process in the multiple systems of the body. Here the chief concern is related to early diabetic brain changes leading to primary complications namely encephalopathy, which is a direct metabolic perturbation related to hyperglycemia due to insulin deficiency, and the secondary encephalopathy complications are due to micro and macro vascular changes occurring in due course of the disease.

The diabetes in the early age of the childhood shows adverse anatomical, physiological and biochemical changes. This metabolic disturbance interferes with the complete morphological maturity of CNS. The onset of these changes are initiated by the constant and excess metabolic overload of circulating glucose, which takes abnormal pathways both in insulin dependent and non insulin dependent tissues of the body. As a result, excess of glucose over load on the brain tissue which tend to produce number of toxic metabolic end products. If these pathophysiological events are not checked at the earliest, in the long run it results in gradual clinical manifestations of childhood diabetic complications. These adverse changes are mainly dependent on the extent of damage which has taken place in the pancreatic islets. The conventional type I DM alerts immediate insulin treatment, but the initial pathological changes may take time to show the effects of absolute metabolic derangement, later which can show the overt symptoms of insulin deficiency. To test the prevention and curative effects of these complications with herbal extracts, one month and two months old young postnatal diabetic rats were selected in this research.
This experiment aimed at showing the morphological changes in the diabetic and post treatment changes in the young diabetic brain. It is a practical challenge to induce the diabetes in young rat model and to study the brain changes. The most advanced techniques have limitation to reveal the clear data on this event. Advanced high resolution of MRI images analysis has revealed that there are some volumetric changes occurring in the developing brain. The developmental and its morphological brain volume changes were normally seen due to increased grey matter density in the cortex. This has showed increased prefrontal brain volume in normal control groups. In contrast to this the diabetic rat brain changes were witnessed with reduction in the size of the brain as observed during dissections. Probably, the drug induces favorable changes directly on the brain cells or indirectly taming the hyperglycemia and may lead to increased number of cortical and hippocampal neurons. Such similar favorable effects in our experimental parameters may influence memory and cognitive functional behaviors in the children.

The conventional notion about the stable number of neurons in the human brain is contradicted through number of advanced studied by using rat models. There will be a drastic postnatal death of neurons and glial cells followed by regeneration within few weeks after the birth. Any metabolic stresses on brain cells are most likely to affect the natural modifications, and at the same time such events are influenced by natural Nootropic agents. The experimental drugs were chosen by considering their two important properties to examine the changes on frontal cortical and hippocampal neurons, and subsequent changes in the pancreas and adrenal gland. The rat brain undergoes postnatal remodeling in an interesting fashion. The neurons undergo apoptosis which is followed by regeneration in a sequential pattern. This phenomenon was studied by using some of the radioactive markers which have shown the
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possibility of addition of newly generated cells in the postnatal periods, unlike our conventional concepts. The interesting modifications were seen in the cerebral cortex and hippocampal regions which is a base for selecting these two important areas in these experimental models. These areas are proved to be the most important regions for effective cognitive function. In order to support this, the numbers of viable neurons were counted in the frontal cortex and the hippocampal region by considering the changes in the brain cells. The quantitative modifications which occur during period between 25-60 days are found to be negligible and their number is relatively stable to consider for quantitative analysis. These observations can be correlated with high discrimination in the number of viable neurons in cortex and hippocampal regions, as seen in young control and other treatment groups.

In the recent few decades research on DM has taken greater pace to achieve effective treatment to benefit mankind. Yet bio-molecular studies, cell line studies, culturing, stem cells research, etc. are practiced this day to find an effective treatment. In spite of much advanced research practices, the evidence of animal experimental research is considered as strong base, as it gives its valuable basic input regarding drug action on the biological system. The inductions of stable diabetic state in the animal experiments are really challenging ones to achieve, because of their limitations. The chemical induction of the diabetes is usually practiced in the field of medical, biomedical, pharmaceutical etc. Chemicals like Alloxan and streptozotocin were widely used chemicals in diabetic experiments. Alloxan is a highly toxic chemical widely used some times before the streptozotocin usage was realized. The Streptozotocin is comparatively less toxic and it can be used even on the neonatal rat experimental studies by considering more effective induction of diabetes with fewer death rates. The diabetogenic chemical is very expensive; it should be
obtained in a fresh form, not to be exposed to air or higher temperatures and should be stored and handled in cold atmosphere. When they are dissolved with the buffer or saline they should be injected immediately, else they may get oxidized even before administration. In vivo the half life of streptozotocin is about 4-5 minutes duration. The route of administration is very important to achieve targeted effect. It is must to inject the drugs like streptozotocin by using freshly prepared citrate buffer preferably in chilled form to obtain effective results. Altered pH of these buffers can render the drug useless, as effective pH range fluctuates with a very narrow margin\textsuperscript{55}.

Rat model shows the pancreatic damage in the islet cell in the absence of autoimmune antibodies. These rats can survive without insulin administration because of partial damage in endocrine part representing the initial stages of early onset of Type I diabetes in early childhood. This shows glucose intolerance through higher fasting glucose levels. These changes were observed in diabetic controls showing histological evidence of structural change associated with higher (>200-400 mg/100 ml) fasting blood glucose levels supporting the impact of metabolic derangement\textsuperscript{46}.

There is a direct relation existing between the age of the rat and the activity of chemical used in diabetic induction. When the response of 3 weeks young rats were compared with one year old rats, they showed high discrimination in attaining the diabetes after the administration of streptozotocin. This could be due to least exposure of the body towards different pathogens with the advancing age. The preparation of our body immune system to fight against the invading organisms on exposure towards antigens. In this context, the Hygiene Hypothesis holds to be a good co-relation in this regard. It was found that the children grown in more sophisticated and hygienic environment are most likely to be the victims of early childhood exposure to infections and they are easily affected with susceptible infection causing pancreatic
damage. This shows that the importance of early childhood immune modification which occurs on exposing the body towards infections. Most of the diabetic experiments by chemical induction mimics IDDM because of their target are to destruct the endocrine part of pancreas. The chemical induced diabetes targeting the induction of DM is a difficult task to achieve because of its impartial effect on whole pancreas where its effects on exocrine part is less stressed in the literature. However microscopic observation in this aspect has shown some changes when compared with control groups. The chemical damage to both exocrine part and endocrine part of the pancreas may contribute to a large extent of metabolic derangement leading to disruption in pancreatic secretary activity which may result in acceleration of metabolic derangement. These overlapping pathophysiological events may worsen the overall metabolism.

The diabetic rats were selected for preventive and curative treatment. The preventive drug therapy was intended to interfere with the early onset of adverse diabetic changes. This model had the advantage to test the benefit of early drug therapy, before causing relatively stable changes in the selected parameters and accordingly the results were appreciated.

The curative treatment therapy was started 30 days after the reconfirmation of stable diabetic condition. Where previous trails are substantiated the impact of glucose derangement need to take about 3-4 weeks duration. This treatment free duration can induce appreciable adverse structural changes on the brain cells including hampered dendritic arborization, chromatolysis, cell shrinkage, air vacuoles or cracks etc. in the cortical and hippocampal area. This was considered as late and mature change happening in the diabetic patients without treatments. The pancreas showed islet cell disruption and hypertrophic changes in its acini; and adrenals
showed degenerative changes like medullary cell hypertrophy and hemorrhagic infarcts. The late treatment interference at the end of 30 days treatment have shown significant comparable changes with age matched control groups with early (preventive)treatment intervention.

At the end of 30 days treatment, groups with early (preventive) and late (curative) treatment intervention has shown significant, comparable, changes. The conventional notion regarding the permanent and irreversible adverse changes in the brain cells were taken into the consideration to test the early and late interference effect of these herbal treatments in case of young diabetic model, on frontal cortical and hippocampus neurons. They are considered as important areas involved in higher functions of brain including memory and cognition. In this case a reasonable effect of prevention against advancing adverse changes and satisfactory recovery in the curative treatment groups were noticed.

The two herbs with diversified action were selected for the experiment, *Clitoriaternatea* is known for its nootropic and antihyperglycemic activity. The *Salaciachinensis* is a well known drug used mainly in antidiabetic treatment. Our experimental hypothesis was to prove the effect of these two herbs administered individually and in combination of juvenile diabetes, by the activity of phytochemicals present in the crude root extract of *Clitoriaternatea* through its antihyperglycemic effect. The *Salaciachinensis* is showing antidiabetic effect and this drug action may check the adverse effects of excess of circulating glucose on the brain cell, along with their preventive and curative effects on pancreas and adrenal glands in the young diabetic rat model.
The root part was chosen as it is the main part on which the survival of the entire plant depends. The root is rich in all types of nutritive chemical constituents essential for the growth and viability of different parts of the plant. The gross root absolute extract was used in this experiment. The safety of these herbs was tested through the toxicity study. The study showed greater safety margin up to >2000-5000mg/kg body weight. Our experimental administrations of these extracts in all the treatment groups were within safety range, with the dose of 100mg/kg body weight. All these drugs were collected from their natural habitat showing the least ash value, which may suggest that these drugs have the minimum inorganic components which may influence the drug action.

Out of several types of extracts absolute alcoholic extracts of above mentioned herbal roots were chosen, because of their universal solvent property, which can protect the extract from the degenerative changes even in long term storage. Before preparing absolute alcoholic extract, initially the herbal root powder was defatted completely by using petroleum ether. This process ensures the undue interference load of fat metabolism in the herbal extracts on oral administration. In future such defatted extracts can be subjected to high performance liquid chromatography (HPTLC) analysis for the identification of different chemical compounds.

Usually, the type I DM needs parenteral administration of insulin. It is conventional practice that the type I diabetes inevitably requires the insulin therapy, but in this case oral antidiabetic therapy was used as it brings gradual changes by affecting the absorption of the glucose from the gut or through any other mechanism, which may prevent the undue excess load of circulating glucose which in turn causing less burden on the endocrine part of pancreas. In other ways, these drug constituents may affect directly or indirectly on the nervous tissue itself.
The change in quality and quantity of food habits of present generation has drastically changed when compared to past. Sedentary work and lack of physical exercise has adversely influenced the food habits. The adulterated, refined and modernized food consumption is becoming the root cause for number of disorders. The consumption of excess of carbohydrates is leading to high circulating blood sugar levels which is gradually showing its load on the endocrine part of pancreatic cells and in the long run leading to inefficiency in handling the same. This effect may gradually lead to subtle Prediabetic changes in the tissues which may bring gross adverse changes recognized as clinical signs and symptoms. Obesity is becoming an important precipitating factor in young diabetic individuals and the same in adults can lead to number of morbidity from simple neuropathy to nephropathy. It has been debated during the last decades whether asymptomatic, unrecognized diabetes or even to a lesser degree of hyperglycemia in random samples indicates increased risk of Cardiovascular Disease (CVD) and death. However, conventionally the investigator who studied the association between hyperglycemia and the development of diabetic complications mainly focused on fasting glucose levels. Hence rats showing Fasting glucose range between 200-400mg/100ml as stable diabetics. In diabetic studies, it is generally recommended to start with simple tests which can provide effective reproducible results without occupying much time. Thus euglycemic animals are used for testing potential oral hypoglycemic agents and are still a valid screening method to assure the basic antidiabetic effect of a drug. Large interventional studies have shown that achieving and maintaining near normal glycemic levels can reduce the risk of microvascular and macrovascular complications in type II diabetes. The postprandial blood sugar control is equally important to prevent its long term complications. Controlling the blood sugar levels by changing our life style and food habits along
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with the rational use of cost effective, easily available herbal supplement in our routine life is an essential need to tackle lifestyle related metabolic disorders. The WHO (World Health Organization) Expert committee recommended and also highlighted the investigation of antihyperglycemic agents from plant origin which are used under traditional medical practice for the treatment of diabetes mellitus. In the glucose tolerance test (GTT) (Table-2 and 3) a drug called Saptharangi (Salaciachinensis W.) which is used generally as anti diabetic agent was chosen and another drug Shankapushpi (Clitoriaternatea L.) which belong to Medhyarasayana (Brain tonic) to support the brain cell metabolism was also chosen. The above mentioned plant extracts used in combination retainsits enhanced postprandial blood glucose tolerance at the end of 90 minutes of time when compared with individually administered extracts. This could be due to bio-molecular drug interaction mechanism which indicates that these extracts in combination are more efficient in achieving the low glycemic index during the post prandial period which can reduce the abrupt high glucose load on the endocrine part of pancreas and also by channelizing the glucose through any other possible routes. By considering such effects, these herbs are well known and also human friendly, easily available and cost effective source for treatment in number of disorders. Even today 60% of world populations rely upon traditional medicine, and the world’s oldest medical sciences like Ayurveda and traditional Chinese medicine have mentioned number of herbs and herbal formulations for the maintain of the health in an healthy individual and to treat the disease. These herbs are not only among such vital drugs but are freely available in the nature. The Salacia species of herbs are a well known for antidiabetic action and have shown a significantly enhanced postprandial glucose tolerance. The other recent experimental drug trials supported the isolated compounds like Mangiferrin from the
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Salaciachinensis W. has shown significant decrease in blood sugar levels along with increased insulin content in the body, which supports the rationality of its ethnobotanical usage since thousands of years. The gross study trials by using the aqueous extracts of leaf and flower of Clitoriaternatea L. in diabetic rats have shown significant reduction in the levels of blood glucose along with reduction in glycosylated hemoglobin levels, and at the same time there was increased serum insulin to nearly normal level is suggestive of its antidiabetic activity. These observations support the multifaceted action of single drug therapy.

Probably, the natural herbal supplements can modulate the immune mechanism which is an important event and needs to be tackled meticulously. Some experimental outcome related to herb Clitoriaternatea showed modification in the Humoral and Cellular immunity. Its immune suppression activity has significantly reduced the primary and secondary antibody titers. Its immune modulator activity indicated through reduced cell sensitivity and phagocytosis.

Administration of root extract of Clitoriaternatea may be an important interference in the young and early recognized diabetes, where the immunity of an individual is wrongly driven by the self antibodies against their own biological components. The Phytochemicals like flavonoids and phenolic compounds of Clitoriaternatea root extracts can be trailed in autoimmune dominated young diabetic experiments. Probably, our experimental outcome might suggest such similar effects.

The salacia species plants have shown effective anti-obesity and antihyperglycemic effects. Which could be an effective remedy to treat the metabolic disorder where the abnormal lipid metabolism can be tackled with better results.
Generally the blood glucose lowering activity of herbs are attributed to the presence of phenolic compounds, Flavonoids, Terpenoids, Coumorins etc., as they bring down the glucose level effectively and significantly indicating that the traditional use of certain herbs in diabetics contains some essential phytochemicals can increase the glucose tolerance capacity\(^\text{101}\). Such drugs are need to be identified, isolated and tried in advanced research set up to understand their mechanism to formulate a new drug for early childhood diabetes. The overall results of this initial evaluation drugs on glucose tolerance assures that these drugs may not cause drastic hypoglycemic impact even when they were administered in combination. Probably the 30 days administration of these drugs in all treatment groups might support the tissue recovery on the endocrine part of pancreas in better way, which may be responsible for showing the normal fasting glucose levels at the end of 30 days of preventive and curative treatments. This observation supports the benefit of long term oral antidiabetic herbal treatment by using these drugs.

This experiment also leads to some observations and findings. In the experiments animals showed normal FBG after the administration of diabetogenic drugs subjected to glucose tolerance test (OGTT) after sufficient overnight fasting (Figure-33). Surprisingly, the results have indicated high glucose intolerance. Probably in some suspected cases such normal fasting blood glucose values can be challenged through oral glucose tolerance test to support the factual clinical evidence of pancreatic insufficiency\(^\text{89}\). This supports that, the OGTT stands as a “Hall Mark” to disclose the subtle diabetic metabolic derangement.

The pathophysiology of the cognitive dysfunction in diabetics is not completely elucidated. The hyperglycemia can cause cognitive defects in both type I and type II diabetes. A variety of mechanisms are included under this category, out of
which the metabolic derangements in polyol pathway and formation of advanced glycated end products (AGEs), diacylglycerol activation, glucose shunting in hexosamine pathway are responsible in causing gradual physio-morphological changes. To support this there was an increased sorbitol levels in the cranial nerves, spinal nerves, cerebral cortex and retina as reported in previous experiments. Hyperglycemia was also found to be enhancing the quantity of the reactive oxygen species (ROS) which in turn influences the polyol pathway. In supporting these studies such altered polyol pathway might have influenced the glucose metabolism to attain the cataract like changes in many streptozotocin induced diabetic rats in the curative (late) treatment groups. Probably, these thirty days treatment free period may can be considered to be a potential and substantial one to prevent morbid diabetic changes in unrecognized diabetic individuals at the earliest\textsuperscript{38,39}.

The structural plasticity is an important phenomenon which takes place in the cortical neurons and hippocampus. They are capable of undergoing modification when they are under the influence of adverse metabolism which in turn influence the cognitive functions. The neurons are sensitive to show their response to physical stress, excess of glucose metabolic load, direct effect of drugs or chemicals by showing adverse effects on cortex. However, such reversible changes were observed by rehabilitation of stressed rats have shown an allosteric effect of neurons, as part of reversible changes observed in the brain hippocampal CA3 region in the present study\textsuperscript{50}.

Numbers of electrophysiological and morphological evidences are supplementing the neurological changes in the diabetic rats, which have shown obvious co-relation between functional and structural defects. In case of preventive therapy the early interference of these drugs indicates that the phytochemicals can
control the adverse effect of excess of glucose load on the frontal cortical and hippocampal neurons of central nervous system.

The extent of our drugs supporting the neuronal arborization and the survival of number of neurons in different treatment and control groups were represented in the form of bar charts where higher or lower mean values are indicating ratio of benefit in all quantitative parameter evaluation.

The apical dendritic intersections in preventive treatment (Figure-34 &35) groups PCLT, PSLA and PC+S showed significantly higher mean values(Table-4). Among these the PCLT group changes are much significant than any other group. This observation supports the conventional thoughts about the memory enhancing and neuroprotective property of Clitoriaternatea. At the same time, stunted growth was seen in case of DB group, but insulin treatment group was not appreciated with any prominent positive changes. Simultaneously the supporting effect of Salaciachinencis on the dendritic arborization was also observed in case of apical and basal dendrite branching points and intersections of preventive treatment groups. These observations in PSLA group need to be considered for advanced experiments in future.

None of the apical branching in preventive treatment groups, showed significant values to compare statistically. But when mean values were compared, all three drug treatment groups showed higher mean values suggesting enhanced arborizations. It was supported by findings of others trails where the administration of Clitoriaternatea root extracts at a dose of 100mg/kg body weight have shown marked growth. The experiments have revealed the effects of aqueous root extract of Clitoriaternatea on the acetylcholine content of the rat hippocampus which is clearly indicative of its significant usage in impaired cognitive disorders. This can interfere with memory
enhancing property in neonatal rats and a little impact on its general motor activity. These observations probably suggest the influence of *Clitoriaternatea* on neurotransmitters favoring the cognitive functions. Such effects may support the action of *Clitoriaternatea* on juvenile diabetic rats. Thus, it appears that the *Clitoriaternatea* extract must have brought some diversified changes in the brain which is responsible for improved learning and memory.

The **apical branching** in preventive treatment group where *Salaciachinensis* was used, we have come across the dendrites studded with numerous spines. This effect was a unique observation under the group where *Salaciachinensis* was used individually as a preventive therapy. Though the *Clitoriaternatea* has shown comparatively much significant dendritic arborization, but here we are unable to appreciate any such small emerging spines from enhanced dendritic branchings, unlike the groups treated with *Salaciachinensis*.

The **basal dendritic intersections** and **branching points** in preventive treatment (Figure-36& 37) groups showed significant mean values on PCLT, PSLA and PC+S (Table-5&6). Conventionally *Salaciachinensis* was considered as antidiabetic herb. But this observation may specifically support the memory enhancing and neuro supportive effect, which shows its multifaceted action, and naturally invites further studies in this direction.

The herbal drugs are well known for their multifaceted activity in more than one disorder. To support the multi disease utility of herbs like *Clitoriaternatea*, they were supported by experimental trials, which have indicated its antihyperglycemic effect by enhancing the activity of glycolytic enzymes in the body along with increased serum insulin level. These results are clearly suggestive of their pancreatic
and extra pancreatic effects. The multi system impact of the herbs could be due to the number of compounds present in the parts used. The isolation and identification of such individual compounds for their specific activity needs further detailed evaluation. The assessment of fasting blood glucose in our experimental animals at the end of 30 day’s preventive and curative treatment has shown euglycemic state which could be due to drug effect of *Clitoriaternatea* on endocrine part of pancreas. The preventive therapy with this drug has shown more number of islet cells with least degenerative changes, which may suggest beneficial impact of this drug on pancreatic islets. These observations invite more advanced studies in this aspect.

The idea of experimental curative treatment trial is based on some of the experimental findings which show the unique property of plasticity in the neurons where the reversibility in morphological changes of the nervous system was realized in diabetic animal models. Diabetic control groups have shown much deteriorating changes in the cortical neuron arborization where the neurons are under the severe impact of excess of glucose metabolism on the brain cells. The interference of these drugs as curative therapeutic agents have limitation in bringing back possible recovery changes in the degenerating neurons. Thus it clearly correlates the lack of reorganization of diabetes and initiation of antidiabetic therapy can bring adverse effects, which can lead to early cognitive inabilities in a child where central nervous system was severely affected.

The apical dendritic intersections in curative treatment groups (Figure-38, 39,) including CCLT, CSLA and CC+S have shown significant results (Table-7). But diabetic control groups showed stunted growth in the basal dendrites. The group treated with CSLA showed its least impact on these changes which may show the
limitation of the drug action or dominated irreversible changes in the diabetic neurons.

None of the **apical branching points** in **curative treatment** groups, showed significant values to compare statistically, but the higher mean values were appreciated in all three treatment groups(Figure-40).

None of the **basal dendritic intersections** in **curative treatment** groups have shown significant mean values to compare statistically. But highest mean values in PC+S treatment group showed an excellent growth pattern. This could be due to combined action of different phytochemicals in this drug combination.

The **basal branching points in curative treatment group** the CSLA,CC+S and DB has shown significant mean values, but the remaining three experimental groups have showed almost similar extent of changes(Table-8).Among the number of body organs, the entire brain is not insulin dependent one, except hypothalamus, which is insulin dependent. The satiety centers, requires insulin. In its absence these centers will constantly stimulate the hunger, in spite of taking the food frequently causing untamed desire to take food. The activity of hypothalamus has its direct influence on the adrenal glands through HPA axis to handle the stressful situation. The direct or indirect influence of stress may affect physio-morphology in the organs of our experimental animals, which need to be taken note of. In diabetic stress the worst affected ones are the insulin dependent tissues. But the constant hyperglycemia will not spare brain even though they are not insulin dependent. The analysis of Golgi impregnated sections of diabetic rats revealed a reduced arborization of cortical and hippocampal neurons, as indicated by the decreased number of branching points and dendritic length. The apical dendritic atrophy is potentiated in all the diabetic rats
which could be due to hyperglycemic stress. The insulin control group showed overall moderate and fair changes unlike changes observed in other treatment groups. The ultimate effect of influence of this herbal treatment on the neuronal arborization can enhance the number of synaptic contact between two neurons. The recent observations of heavy frontal cortical neuronal circuitry in postmortem studies on the great scientist Einstein’s brain correlates with his extraordinary IQ involved in number of inventions. Probably such influence can be brought on cerebral cortex by using drugs of natural origin in the early childhood, which may modify, prevent or reverse the physiomorphological changes in young diabetics. But the much advanced intervention of treatment with these herbs may yield desired benefit in this aspect, especially on the nervous tissue where the completion of myelination of corticospinal tract which generally takes place within few weeks after the birth.

The number of viable neurons and their synaptic contacts are important prerequisite for an effective cognition. They are sensitive to show changes from simple to complex manner against the stressful events. The early diabetes affects survival of number of neuron; this event can be checked by herbal treatment. This effect was observed in most of the treatment groups where increased numbers of viable cortical neurons were appreciated.

In the preventive treatment groups, the number of cortical Neurons(Figure-41&42) in PCLT and PSLA treatment group has shown good support for their survival, except in PC+S, which has shown least survival effect on the number of cortical neurons (Table-9).

Regarding the hippocampal neurons in preventive treatment groups (Figure-43& 44) satisfactory number of their survival was seen in NC, DB and insulin
treatment groups (Table-10). But all three treatment groups have shown their moderate impact. This discrimination between cortical and hippocampal neurons could be due to therapeutic response of cortical neurons when compared with neurons of hippocampal CA3 region.

In supporting to this, the results of initial evaluation of extracts on glucose tolerance in normoglycemic have shown significantly lower postprandial glucose levels at the end of this study. This observation also could be due to the gradual influence of our drugs which might have brought hypoglycemic effect due to combined drug administration continued for a month period. This observation may be correlated with overwhelming response of combined drug administration causing gradually enhanced glucose tolerance.

The FBG level at the end of preventive and curative treatment has shown least blood glucose levels. This effect can be correlated with similar response taking place in patients who are on antidiabetic treatment, where the islet cell recovery can cause hypoglycemia. During such situations the patients are often advised to reduce or stop the medication for some time. Such conditions were usually seen few months after initiating antidiabetic therapy. This is also one of the factors which might influence the brain cells.

The cortical neurons in all curative treatment groups (Figure-45 & 46) have shown good number of viable neurons (Table-11) when compared with other three treatment groups, which have shown least number of viable neurons.

In case of hippocampal neurons in curative treatment group, the CC+S treatment group (Figure-47 & 48) showed good number of viable neurons when compared with other treatment groups (Table-12). This effect could be due to
interference of phytochemicals present in this combined drug treatment on the biological system where already established metabolic derangement was established in the 30 days duration.

Though there are some discriminating findings observed in the results, yet the evaluation of fasting blood glucose at the end of our preventive and curative treatments have shown normoglycemic response(Figure-49 & 50). This response was seen irrespective of preventive or curative treatments in all experimental groups (Table-13 & 14).

In case of Preventive therapy with the individual drug Clitoriaternatea and Salaciachinensis and in Insulin groups have shown histopathological findings where pancreatic tissue was witnessed with improved qualitative changes in endocrine part of the pancreas(Figure-51). It shows treatment support in pancreatic tissue recovery when compared with age matched diabetic controls in our experiments. Subsequently in the curative therapy we could not distinguish any significant improvements in the pancreatic tissue, in any of experimental groups (Figure-52).

Though at present an effective modern therapy is available for diabetes but there are limitation regarding safety margin in its dose, side effects, difficulty in routine parenteral administration, drug resistance, affordability etc.

The stress is an event which can show its adverse effects on nervous and endocrine system. But such changes are often influenced by diet, diurnal changes, seasons, physical stress etc. In most of the experiments the animals are restrained and deprived of their natural habitat including their movement, food intake, sexual behavior etc. which might bring some sort of stress in them. Such effects may be
reflected through adrenal gland changes and it is applicable to all experimental groups as they are placed in the same environment. The role of the adrenal gland is considered generally during the stressful events occurring during lack of endogenous insulin or metabolic ketoacidosis. Here the body needs energy source from different components other than carbohydrates. In the absence of insulin, it exerts metabolic stress on the adrenals. In the prevailing situation the adrenal gland will come into picture by releasing large quantity of stress hormones into the circulation. Thus constant effect will try to supplement the energy resources by inducing hyperglycemia. This adoption effect may cause a sort of work hypertrophic changes in adrenal gland. There are some experiments which still support this notion, but the literature evidence in this regard is much limited.

Significant appreciable changes were not noticed in the adrenal cortical region in both preventive and curative treatment groups (Figure-53 & 54). This observation may be due to young age of the rat or it could be due to the lack of influence from higher centers of the brain like hypothalamus on adrenal gland, where its cell metabolic activity depends on availability of insulin and age of rat. But in case of preventive and curative treatment groups, the medullary component has shown hypertrophy along with hemorrhagic infarcts. In addition to above observation, some mild adverse changes were appreciated in the medullary components with hemorrhagic infarcts, which was seen in all experimental groups including normal controls indicating the stress in all the experimental animals (Figure-55 & 56).

The experience in the experimental management of the animal diabetic models will give the virtual understanding of the disease in many aspects. The great challenge in the young diabetics lies in adjusting the appropriate dose of insulin and its delivery. Generally in mild diabetics, it is around 0.5mg/kg body wt., the same dose was
adopted to treat the diabetic control animals but patients with severe ketoneuria along with associated symptoms like weight loss, may need higher dose. The delivery of appropriate insulin dose in the young children can even threaten with the episodes of the hypoglycemia. These episodes can occur during the night hours without warning. One of the great threats in the course of insulin treatment is an overt response of islet cells releasing endogenous insulin over a period of months or years, which is more commonly seen in diabetics. This effect could be due to recovery changes in the endocrine part of the pancreas. Clinically this can be recognized through existing signs and symptoms, which often force one to stop the insulin or oral intake of antidiabetic drugs to avoid overt hypoglycemia. Such attacks need quick attention in young diabetics. To avoid drastic adverse effects the slow and sustained action of herbal treatment may be a boon for juvenile diabetics.

The initial administration of the dose around 2units/kg body weight has caused severe impact on the brain cells causing a significant shrinkage of the brain recognized during dissections. On microscopic examination it was obvious that the neurons were showing complete shrinkage in the cortical and hippocampal neurons indicating overwhelming adverse response with slight higher insulin dose. Unlike our natural antidiabetic drugs, the synthetic drugs have the capacity to act vigorously; slight negligence can lead to severe and drastic adverse impact on the body especially in young diabetic children. A slight over dose of the insulin or repeated administration of insulin by mistake, can cause severe hypoglycemia, which is considered to be more dangerous than hyperglycemia. These episodes may be efficiently managed to some extent in the adult diabetics, but the same in case of juvenile diabetics needs a careful monitoring. In addition, the juvenile diabetics need proper guidelines, education and monitoring to avoid such dangerous situations. In type I diabetics it is reported that
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hypoglycemic attacks are quite common where there is a counter regulatory hormones like glucagon mechanism which is found to be weak. Out of number of hypoglycemic agents the derivatives of herbs from different plant origin are most unlikely to cause the drastic hypoglycemic attacks unlike synthetic drugs because of their slow action by interfering with the rapid absorption of the glucose from the gut. This basic experimental finding will support the superiority of herbal drug treatments with diversified action supporting in juvenile diabetic animal model. The present study needs further detailed evaluation on multi faceted action of herbal root extract of Clitoriaternatea Linn. and Salaciachinensis Wight., to gift a new drug to early childhood diabetics.