Design of Medical Biochemistry Undergraduate Laboratory Based Curriculum to Address Unmet Needs

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Abstract

Background and objectives: Review of the undergraduate medical curriculum in India is not done regularly. Strengths and weaknesses need to be identified in order to develop strategies to improve the curriculum. Objective was to critically appraise, modify and implement biochemistry laboratory based curriculum for undergraduates as an endeavour for critical introspection and to set a platform for change.

Methods: A self-administered questionnaire for faculty and interviews for students were used to identify needs which would help to create an educational environment conducive to change and innovation. The existing undergraduate biochemistry laboratory curriculum was analysed using Kern's framework, triangulating the qualitative and quantitative data, to develop a modified curriculum. As a pilot study, a checklist was made for one laboratory unit and the faculty was trained to use it. Kirkpatrick's model was used for evaluation of training.

Results: The major strengths and weaknesses of the curriculum were identified. Accordingly, the objectives, teaching - learning methods and assessment strategies were aligned. For the first time, measures for honing and assessing interpretative skills of students were incorporated. The results showed that three levels of Kirkpatrick's evaluation model were achieved for the training of the checklist. Paired 't' test was used to check the differences in marks of students before and after applying the checklist of marks allotment. The mean score of the marks of one laboratory experiment unit (urine report) after applying checklist pattern (M=9.18) was compared with the mean score of the marks without applying checklist pattern (M=10.12).

Conclusions: Evaluation of curriculum provided a snapshot of the strengths and weaknesses of current biochemistry practical curriculum and also guided improvements particularly with regards to inclusion of more clinically relevant curriculum with group based learning. The data derived from this study will help to make suggestions to the decision making bodies i.e. Medical Universities (both national & state based) in India.

Keywords: curriculum design development and implementation, laboratory exercises

Background

A curriculum is a planned educational experience that encompasses behavioural instructional methods and the actual experience of the learners (Green, 2001).

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The main intention of curriculum design is to foster goals, the academic development of students (Rethy & Khoo, 2001). The curriculum is not a static system but in fact is a dynamic, interactive process, whereby changes of one step will affect and require adjustments of other steps (Brodsky & Newman, 2011). It is a cvcle which involves development through needs assessment, design and implementation phase (Peyton, 1998). Ideally the medical curriculum should empower medical students with a broad base of knowledge and practical skills that help them to become good clinicians. As the physicians requirement for knowledge and skills evolve, need for new curriculum is often felt to incorporate new knowledge and competencies (Epstein & Hundert, 2002).

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Hence, there is a need for medical curriculum to be evaluated, corrected and sent through repeated levels of changes.

The knowledge of biochemistry is important for the diagnosis and management of various illnesses. Biochemistry is a basic science subject which is taught in the first phase of the undergraduate medical curriculum in most countries. An improvement in the teaching learning process can be planned by pilot implementations and by improvements in the curriculum (D'Souza *et al.*, 2013).

Clinical Biochemistry Faculty has often debated that the contents, methods of teaching, and curriculum organization of training in clinical biochemistry in India needs to be modified (Mishra, 2000). Opinions have emerged through informal discussions with interns and final year medical students that the current undergraduate clinical biochemistry laboratory curriculum in Indian Medical Schools is not aligned to the modern trends in clinical biochemistry and laboratory medicine and does not reflect the actual content of the rapidly evolving discipline. Besides, at national level conferences formal meetings with senior biochemistry faculty members for curriculum discussion have also yielded concern for a revision in the undergraduate laboratory curriculum.

As an initial step, a formal needs assessment conducted by collectina Clinical was Biochemistry Faculty (from Medical Colleges of Maharashtra. India) views using а questionnaire as an endeavour for critical introspection. It endorsed that the on-going clinical biochemistry undergraduate practical curriculum implemented in the institute was not in alignment with learning outcomes and that it did not encourage active learning along with critical thinking and problem solving skills. There were a number of qualitative experiments that were rated as 'irrelevant'. The results of the curriculum evaluation suggest a need for restructuring of laboratory based biochemistry curriculum and introduction of a modified curriculum with more clinical relevance.

Through this survey, it was observed that outdated practical curriculum is a very serious biochemistry issue affecting clinical undergraduate education not only in Maharashtra but in all Indian medical schools (Dandekar et al., 2012). Also, students' perceptions about the laboratory based curriculum, different topics within the subject and their suggestions have not been reported

in the recent times. Therefore, a need to evaluate and restructure the curriculum towards the newer trends in biochemistry and laboratory medicine was felt.

The aim of this study was to critically appraise the clinical biochemistry laboratory based curriculum by seeking student's perception, find out its strengths and weaknesses in order to lend more credibility for modification and to set a platform for implementation of improved curriculum by decision making bodies.

Methods

This study was aimed to analyse and modify the laboratory present biochemistrv based curriculum at medical colleges of Maharashtra. Institutional academic ethics committee approval was sought and the same was gained. This study design was guided by three steps-1) Critical appraisal of current laboratory based biochemistry curriculum and identification of areas of modifications 2) Development of new curriculum and 3) Implementation.

A concurrent mixed method strategy was used in which quantitative and qualitative data were converged in order to interpret the overall results (Creswell, 2013).

A) Appraisal

For systematic appraisal of the biochemistry undergraduate practical curriculum, the authors sought faculty view through a questionnaire, examined the course document, and conducted interviews with students. Changes required in the present curriculum (additions and deletions) were sought, individual assessment evaluation was done and views about the new assessment pattern and marks distribution pattern (evaluation tool) for a particular experiment's evaluation were obtained (Dandekar *et al.*, 2012). The details of this curriculum are available on the university website (MUHS curricula I).

The present study reports the following- 1) Analysis of current curriculum according to Kern's model of curriculum evaluation framework (Kern *et al.*, 2010), and 2) Student's perception about current curriculum.

Perceptions of students about the current curriculum were sought by Senior Biochemistry Faculty of Institution. For this purpose, semistructured interviews were conducted to identify student's needs which would help create an educational environment conductive to change and innovation. Fifty interns and postgraduate students were included in the study as it was felt that they would be able to elicit the shortcomings of the curriculum while diagnosing and treating patients. Some of the questions asked to the students were: 1) What aspects of the current curriculum appear to be relevant to their role as a doctor? 2) What part of the curriculum needed to be changed? In these interviews students also discussed their educational and training experiences and made suggestions.

Interview data were analysed qualitatively. Open ended comments on the course evaluation survey for students were analysed through thematic coding with attention to generated themes. Thematic analysis is a qualitative data analysis strategy by which qualitative data are segmented, categorized, summarized, and reconstructed in a way that captures the important concepts within the data set (Braun & Clarke, 2006).

Key points were extracted from student's comments and themes were generated. These themes were used for new curriculum designing (Table 3).

In the final step, triangulation of data from all the sources was done to prepare a modified curriculum. Triangulation is the process of "corroborating evidence from different individuals, types of data and methods of data to support the theme" (Berk, 2006).

B) Modified Curriculum Development

After formal teachers and learner's need assessment and curriculum evaluation through Kern's framework, a new modified curriculum was prepared which involved:

- Learning outcomes/objectives (knowledge, skills and attitudes)
- Content
- Teaching and learning methods
- Assessment methods

In this modified curriculum, objectives, teaching- learning methods and assessment strategies were aligned using John Biggs constructive alignment theory (Biggs, 2003).

C) Implementation and Monitoring of Evaluation Tool (Checklist)

A pilot implementation of one of the evaluation tools was conducted to gauge the effectiveness and validity of new ideas (McKimm, 2007). A checklist which was validated by the faculty for one laboratory unit was used for the practical assessment evaluation and the faculty was trained to use it (Figure 1).

Particulars (Urine Report)	Marks allotted
Physical characteristics (Writing + performing) Specific gravity Rest of the parameters such as colour, odour, etc	1 1
Chemical constituents (writing + performing) Proteins, Glucose Blood Bile salts and pigments Ketone bodies	1 1 1 1
Clinical interpretation of the positive constituents (generally we keep 2 positive constituents)	2
Viva Voce Report presentation format	5 1
Total	15

Figure 1: Checklist for Urine Report Experime

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During the assessment for one of the units, (formative assessment), 6 teachers were requested to assess the urine experiment report by using a checklist pattern and also by using the conventional method. Answer sheets of 49 students were randomly selected for the process. For data analysis, SPSS software version 17 was used to calculate the t–value, pvalue and mean.

The implemented programme was monitored using Kirkpatrick's learning evaluation model was used to evaluate training given to faculty and effectiveness of checklist. Reaction was assessed by analysing feedback form filled by the faculty. The questions included in the feedback form were: 1) Have you used a checklist for practical before? 2) If yes-for what? 3) Did you find using this checklist convenient? 4) Were you able to finish assessing question more effectively because of the checklist? Learning was judged by comparing the student's scores with and without checklist and behaviour evaluation was done through observations (Kirkpatrick, 1998).

Results

1) Curriculum review as outlined by Kern's Framework

The Kern's framework was used to review the learner and program characteristics, learning objectives, instructional strategies, feasibility and sustainability and effectiveness. After evaluation of curriculum, several strengths and weaknesses were found in the current practical curriculum (Table 1).

	Kern step	Data sources	Strengths	Weaknesses
1)	Problem identification and general needs assessment conducted	Syllabus content and student- faculty interview Available on MUHS website- www.muhs.ac.in		 No relation of current curriculum to public health and epidemiology. Not focused to improve knowledge attitude and analytical skills needed in modern practitioners. Clinical importance of the biochemical tests is neglected. Lack of sound scientific base for prescribing of biochemical tests as a
2)	Needs assessments with targeted learners	Syllabus, content, student-faculty interview and Institutional magazines- Shidori and Drishti.	Some undergraduate programmes are organized in the institute where focus is given on the student's personal development (Cognitive, Affective, and Psychomotor) and which can help to know the characteristics and proficiencies of students.	 No evidence that these programmes are being used in targeted needs assessment for curriculum designing. No opinions are taken from students about learning strategies (teaching time, duration, learning method).
3)	Goals and objectives	Course document (Practical syllabus)		 Deficiencies were found with respect to format, organization and contents. The layout, language and organization of the course objectives were inconsistent. Course goals were not explicitly stated. The goals and objectives were not matching with modern needs which also reflected in the assessments, instruments and procedures included in the current syllabus.

4)	Educational strategies	Course documents, student-faculty interview data		 Strategies did not include clinical problem solving based on the biochemical tests, group learning and discussions. No exposure of students to hospital environment, hospital clinical laboratories and patients. No elective strategy was used, all students have same curriculum. No case presentation and case discussion.
5)	Implementation	Course document, Practical syllabus	 Sufficient numbers of hours are available to deliver it in an optimal way. Well established lab, and dedicated faculty members, Administrative support is available. Seminars. Sufficient resources – (faculty, AV, computing, secretarial and other support staff, patients) Facilities: (internet, instruments & equipment, LCD, projectors, seminar hall etc to deliver the curriculum. 	 No group learning sessions, Time distribution for practicals is not correct. Active learning is not optimized. Lack of guidance and direction to the teachers caused an inconsistent understanding of the course's objective. Approach to teaching does not uses laboratory instruments and a clinical presentation format. No strategies (pilot or inphase) to implement the new ideas to improve the curriculum.
6)	Evaluation	Student practical examination data, Group discussion from students and faculty		 Lack of suitable methods to evaluate clinical knowledge and skills of students. No self-assessment procedure (Lack of feedback to the faculty about their performance as teachers). No feedback is taken from students about the teachers, teaching techniques etc. Objectives and students examinations are not aligned. Lack of Objective Structured Practical Examination (OSPE)) and Objective Structured Assessment of Technical Skills (OSATS). No structured checklists to increase reliability and validity. No audit from university to check the performances of students and faculty. No formal meetings and group discussion or teaching sessions to revise, improve update and analyze weaknesses of curriculum.

2) Student's Perceptions

Interviews with students showed that commitment, dedication and clinical experience

of teaching faculty, good infrastructure and facilities were the major strengths of the curriculum. A number of weaknesses were also identified and summarized (Tables 2, 3).

Data source	Strengths	Weaknesses	Exemplar quotes
Students interview	 Dedicated faculty members. Sufficient facilities and laboratory set up in the department. 	 Traditional manual methods, No contact with the hospital and patients No learning of applied applied divisal 	• Our practical curriculum seems to stress upon the traditional manual method of metabolite estimation.
		 aspects of clinical biochemistry, No demonstration about the modern instrument and reagents handling. No case history pattern to understand the clinical scenario of the 	 Practical sessions should be more interactive. Students should be given example of patients' urine/blood reports and asked to discuss about the probable diagnosis.

Table 2: Perception of students about the undergraduate biochemistry laboratory curriculum

Table 3: Generation of Themes Form Student Based Interviews

SR no	Themes	Key points	
1	Very brief introduction to role of clinical biochemistry laboratory in hospital settings.	Ambiguity at the undergraduate level regarding use of biological samples for identifying abnormalities. Equipment commonly used for analysis of biochemical parameters.	
2	Inclusion of recent advances in diagnostic methods and analytical instruments.	No inclusion of new and advanced biomarkers. No synchronization with the modern analytic methods.	
3	Clubbing of clinical case taking & diagnostic evaluation.	Minimum teaching of clinical cases. Less early clinical exposure	

3) Curriculum Modification

After identification of the weaknesses of the present curriculum and triangulating data from all sources, an attempt was made to design a modified curriculum in which the objectives and content were structured and aligned with teaching learning methods and assessment strategies (Table 4). For the first time, measures for honing and assessing interpretative skills and problem solving skills of students were incorporated. The modified curriculum was also compared with the present curriculum at the University (Table 5).

Table 4: Alignments of objectives with teaching learning methods and assessment strategies

SR No.	Learning objectives/outcomes	Teaching and learning activities	Assessment
1	At the end of practical class, students shall be able to- - Choose appropriate biochemical tests for confirmation of diagnosis of the disease condition.	Preparation of cases Group Discussion	Short cases history to choose relevant biochemical tests for the diagnosis of diseases. Discussion of the clinical relevance of the analytes estimated

2	Interpret laboratory results in patients in order to make a laboratory diagnosis or confirm a clinical diagnosis of disease.	Demonstration Small group sessions	-Case histories with laboratory results for interpretation of laboratory results in patients with specific disease condition.	
3	Explain the principle of functioning of diagnostic instruments and instruments commonly used in a biochemistry laboratory and their application.	Hands on training and tutorials	-Spot and discussion on laboratory instruments. OSCE Station	
4	Interpret electrophoretic patterns associated with different disease conditions.	Demonstration	- OSPE observation, marking, checklist	
5	Apply principles and knowledge of nutrition to be able to advise patients on optimal diets in health and disease	Tutorial	-Applied aspects of nutrition (spots and discussion).	
6	Identify abnormal constituents of urine and carrying out relevant tests and interpretation and discussion of the results.	Demonstration, tutorial and practicals	-Analysis of unknown specimen of urine to detect abnormal constituents of urine. -Checklist	

Table 5: Comparison of current and modified course objectives, content and practical assessments

Sr. No.		Current	Modified
1	Objectives At the end of the course, the students shall be able to – At the end of practice		At the end of practical class, students shall be able to-
		 Make use of conventional techniques/ instruments to perform biochemical analysis relevant to clinical screening and diagnosis. Analyse and interpret investigative data. Demonstrate the skills of solving scientific and clinical problems and decision making. Suggest experiments to support theoretical concepts and clinical diagnosis. 	 Choose appropriate biochemical tests for confirmation of diagnosis of the disease condition. Interpret laboratory results in patients in order to make a laboratory diagnosis or confirm a clinical diagnosis of disease. Explain the principle of functioning of diagnostic instruments and instruments commonly used in a biochemistry laboratory and their application. Interpret electrophoretic patterns associated with different disease conditions. Apply principles and knowledge of nutrition to be able to advise patients on optimal diets in health and disease.
2	Assessments	 -Quantitative assessment of blood sugar, urea and liver function test, amylase, uric acid calcium and CSF sugar. -Qualitative or quantitative estimation of biochemical parameters. -Normal and abnormal constituents of urine. Spot identification include- slide identification tests of mono and disaccharides, precipitation reaction of urine, use of instruments, identification of Hb derivatives, GTT, electrophoretogram and chromatogram. 	 Short case histories. Interpretation of laboratory results in patients with specific disease condition. Identification of abnormal constituents of urine and carrying out relevant tests and interpretation and discussion of the results. Applied aspects of nutrition (spots and discussion). Principles of important tests (including dipstick tests) to detect abnormal constituents of urine.

3	Content	Instruments -pH meter, colorimetry, electrophoresis chromatography, flame photometry.	Instruments -pH meter, electrolyte analyser, semi and fully automated analysers, spectrophotometer, electrophoretic equipment.
		Biochemical parameters - tests of mono, di-saccharides, sugar, urea, creatinine, liver function tests, amylase, uric acid, cholesterol, calcium, phosphorus,	Diseases- diabetes mellitus, dyslipidemia, myocardial infarction, renal failure, gout proteinuria, nephritic syndrome, edema, jaundice, liver diseases, pancreatitis, disorder of acid base balance, thyroid diseases, renal
		proteins.	failure, common vitamin deficiencies, anaemia, mono and poly clonal gammopathies. -Plasma proteins (Albumin, globulin) -Energy metabolism and nutrition

4) Evaluation of Pilot Implementation of checklist

In the training given to the faculty for pilot implementation of checklist, three levels of Kirkpatrick's evaluation were achieved:

a) Reaction-Reaction to use of the checklist was obtained from faculty by using feedback form. Significant satisfaction amongst the faculty was felt and their scoring skills and consistency was improved.

b) Learning-Learning was assessed by achieving the uniformity in marking among the

faculty which was measured by comparing the student's scores with and without the use of the checklist.

As a result of comparison of marks, it was found that for the 49 subjects included in the study, the mean score on the marks allotted using checklist pattern (M=9.18) was significantly lower p<0.01 (p=0.005) than the mean score on the marks without applying checklist pattern (M=10.12) (Table 6). This was because the checklist evaluated the students on criteria like attitude reasoning and critical thinking other than theoretical knowledge.

Table 6: Evidence that marks allotment pattern for experiments given in the exam is valid

Marks without checklist pattern (out of 15) (mean) n=49	Marks with checklist pattern (out of 15) (mean) n=49	t -value	p –value
10.12	9.18	2.922	< .005**

(** = significant at the level of 0.01)

Particulars (Urine Report)	Marks allotted
Physical characteristics (writing + performing)	
Specific gravity	1
Rest of the parameters such as colour, odour, etc.	1
Chemical constituents (writing +performing)	1
Proteins, Glucose	1
Blood	1
Bile salts and pigments	1
Ketone bodies	1
Clinical interpretation of the positive constituents (generally 2 positive constituents are kept)	2
Viva Voce	5
Report presentation format	1
Total	15

a) Reaction: Reaction to use of the checklist was obtained from faculty by using feedback form. Significant satisfaction amongst the faculty was felt and their scoring skills and consistency was improved.

b) Learning: Learning was assessed by achieving the uniformity in marking among the faculty which was measured by comparing the student's scores with and without the use of the checklist. As a result of comparison of marks, it was found that for the 49 subjects included in the study, the mean score on the marks allotted usina checklist pattern (M=9.18) was significantly lower p<0.01 (p=0.005) than the mean score on the marks without applying checklist pattern (M=10.12) (Table-6). This was because the checklist evaluated the students on criteria like attitude reasoning and critical thinking other than theoretical knowledge.

c) Behaviour: Faculty used the checklist for subsequent laboratory based assessments indicating change in behaviour while doing evaluation. Impact was noted when the faculty asked for the use of checklist even after the study was over.

Discussion

This study was designed to review current practices in biochemistry laboratory based curriculum and to seal the gaps between course objectives, content and assessments. Multitheory approach and detailed triangulation process for curriculum appraisal, evaluation, development and implementation were used. In concordance with the first objective the strengths and weaknesses of the current biochemistry practical undergraduate curriculum were evaluated using Kern's framework. Major weaknesses found were absence of formal need assessment, case presentation and discussion. The layout, language and organization of the course objectives were inconsistent. Also, no formal discussions and meetings, group selfassessment procedures could be identified. Thus the current curriculum lacked the basic and crucial elements essential for optimal learning.

As the second objective was to reform practical curriculum, it was renewed using Kern's framework and stakeholder's opinions. The changes made, it is hoped, shall help students to get early clinical exposure to develop problem-solving skills and self-direction to ensure that they have active responsibility for their learning process (West *et al.*, 2000;

Dornan *et al.*, 2006; Taylor & Miflin, 2008). So, Kern's framework used in the study, served two purposes. It worked as a curriculum evaluation tool and at the same time it worked as a tool for curriculum modification.

Recreating a curriculum is intimately linked to the needs of learners and society-needs which periodically require re-examination thus emphasizing that need assessment is a critical step (Kern *et al.*, 2010). This study acknowledged that this step was neglected in the present curriculum and further realized the significance of conducting an initial needs assessment in developing clear and meaningful objectives.

For a medical curriculum to be an effective means of learning for today's students, it must be written with knowledge of their priorities, needs and abilities. The way in which this can be best achieved is by the inclusion of current student's opinions in designing a new curriculum. It is by actively seeking student involvement and using their input, that faculties will be able to create a consumer-friendly curriculum (Huppatz, 1996).

As the student's views are indispensable to amend the curriculum their interviews were recorded (Table 4). Generated themes from the interviews were used to prepare new objectives and to modify the curriculum. The deficiencies in curriculum observed by the stakeholders (student-faculty) were identical to those found after Kern's evaluation and included absence of important learning objectives and discrepancies between objectives and content. Also, the objectives were not aligned to teaching learning methods and assessments. Moreover, there was no association between laboratory and clinical practices. Such a needs assessment was also documented in a study where guidelines for biochemistry curriculum alteration were recommended after considering the students views. Biochemical concepts and their clinical conditions were identified as critical steps toward enhancing relevance of clinical biochemistry (Wendelberger et al., 1998).

In our process of curriculum modification, laboratory based curriculum was designed to modify the way biochemistry is taught and assessed. New objectives, content and assessments were set keeping in mind the requirements of a doctor at the end of the undergraduate medical course (Table 5).

Wet and redundant experiments were removed and new experiments were designed to improve clinical and problem solving skills of the students in order to incorporate adequate skills for the execution of diagnostic tests, latest instrument handling was also added which was one of the themes developed after need assessment.

Pilot Implementation of modified curriculum

An organization's prior with history implementing innovation influences that organization's subsequent change efforts (Corbett et al., 1984). No previous history of biochemistry curriculum innovation and implementation could be observed in the institutes. This study is an initiative to innovate and implement curriculum and to encourage periodical innovation process.

In this project, we implemented the innovation as a pilot project because fully implementing curricular change in medical schools to incorporate innovations is a challenge as many factors such as leadership, funding, human resource development etc. affect the process (Altrichter, 2005; Bland et al., 2000). The chief objective of a pilot project is to test the draft curriculum in a small number of training situations and in the context in which the curriculum will be used. This helps to highlight to the curriculum developers whether the curriculum is understandable and relevant to the users and whether it works in practice. Based on these findings, the curriculum can be modified as appropriate to meet the needs of the potential students. Piloting can also assist to create the most appropriate course as often the paper curriculum does not work as expected in practice because of unforeseen situations or responses by students or teachers (McKimm, 2007).

Training was given to the faculty for using checklist of (urine experiment) practical evaluation. Three levels of Kirkpatrick's evaluation were achieved. It helped them to increase their scoring skills and to analyse and improve over all practical skills of students. Uniformity in marking was achieved by using the checklist and faculty used the checklist for subsequent practical assessments indicated change behaviour. Evaluation in of effectiveness of implemented programme are not given due importance as that of their planning and implementation (Rajeev et al., 2009). In this study not only the modified curriculum implemented as a pilot but its effectiveness was also measured using Kirkpatrick's model to assess the usefulness of the implemented programme.

Through this project, as a result of evidence based and collaborative process, a new practical curriculum structure has been developed. It is structured around generated themes from triangulation and designed considering the learning outcomes that describe the clinical competencies to be achieved after completing the practical course. Planning for redesigned biochemistry practical curriculum has been done, implementation has been initiated through our pilot study but institutionalization is still to be achieved.

Conclusions

Though there was a growing discontent amongst the faculty and students regarding the practical curriculum, no steps had been taken to alleviate this. Under these circumstances, it was thought that it would be wise to make small inroads by involving stakeholders in collecting and distilling the strengths and data weaknesses of the curriculum and to offer insights into the ways to modify it. This systematic appraisal will help to lend credibility for change to the curriculum. Therefore our study offers a snapshot of a review on traditional current undergraduate biochemistry practical curriculum of India. The data derived from this study has helped to make suggestions to the stakeholders and other decision making bodies in India.

Authors' Contribution

SD prepared the study design and carried out data collection and data analysis. SM contributed to the data analysis and writing of the manuscript. DM contributed to reviewing and editing of manuscript. All the authors have reviewed and approved the final version of the manuscript.

Competing Interests

The authors declare no competing interests.

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